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בקשה לפטנט
Application For Patent

אני, (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)
I (Name and address of applicant, and in case of body corporate-place of incorporation)

G. D. SEARLE & CO., a corporation of Delaware,
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בעל אמצאה מכח ~~דאגא~~ העברה an assignment ~~xxxghtxofxlaw~~ ששמה הוא
Owner, by virtue of ... of an invention the title of which is

(בעברית) (Hebrew)
4-[(5H-אימידזו[c-5,4]פירידין-5-יל)אלקיל]בנזאמידים ותכשירי רוקחות המכילים אותם

(באנגלית) (English)
4-[(5H-imidazo[4,5-c]pyridin-5-yl)alkyl]benzamides and pharmaceutical compositions containing them

hereby apply for a patent to be granted to me in respect thereof
מבקש בזאת כי ינתן לי עליה פטנט

• בקשת חלוקה — Application of Division	• בקשת פטנט מוסף — Application for Patent Addition	• דרישה דין קדימה Priority Claim		
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filed on a previous case P.98090 הוגש בענין קודם				

המען למסירת מסמכים בישראל
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חתימת המבקש
Signature of Applicant

For the Applicants,
DR. REINHOLD COHN AND PARTNERS
By : —

This 12th. היום of March בחודש of the year 1989 שנת

לשימוש הלשכה
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Delete whatever is inapplicable

4-[(5H-אימידזו[4,5-c]פירידין-5-יל)אלקיל]בנזאמידים ותכשירי רוקחות
המכילים אותם

4-[(5H-imidazo[4,5-c]pyridin-5-yl)alkyl]benzamides and
pharaceutical compositions containin them

G.D. SEARLE CO.

C: 77086

FIELD OF THE INVENTION

This invention is in the field of mammalian therapeutics and relates to compounds for treatment of mammalian diseases such as inflammation, cardiovascular disorders, asthma and other diseases. Of particular interest is a class of 5-substituted [4,5-c] imidazopyridines useful for treatment of cardiovascular and immuno-inflammatory related disorders mediated by platelet activating factor (PAF).

BACKGROUND OF THE INVENTION

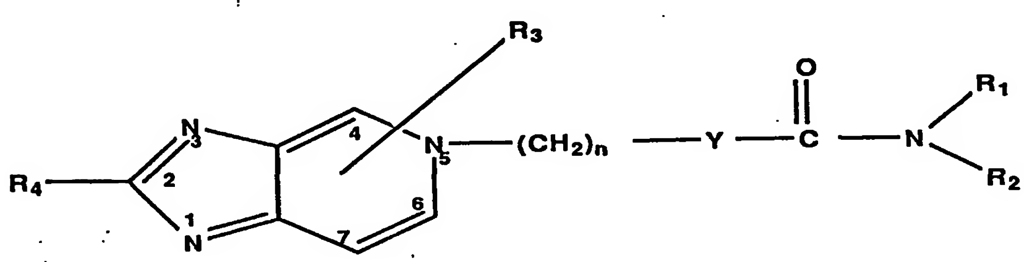
Platelet-activating factor (PAF) has been associated with various biological activities and pathways, thus making it an important mediator responsible for a variety of physiological processes including, but not limited to, activation and aggregation of platelets, smooth muscle contraction, pathogenesis of immune complex deposition, inflammation, and respiratory, cardiovascular and intravascular alterations. These physiological processes are associated with a large group of diseases, such as,

for example, cardiovascular disorders, asthma, lung edema, endotoxin shock, adult respiratory distress syndrome and inflammatory diseases.

United States Patent 4,804,658 discloses a class of imidazopyridine derivatives useful in the treatment of diseases or disorders mediated by platelet-activating factor. The present invention is distinct from this disclosure in that in the present invention the benzamide moiety is attached to the nitrogen (position 5) which makes up the six membered ring of the imidazopyridine ring system as opposed to the disclosure wherein the benzamide moiety is attached to one of the nitrogens which makes up the five membered ring of the imidazopyridine ring system.

Summary of the Invention

The present invention relates to a novel class of compounds represented by the formula



I

or a pharmaceutically acceptable acid addition salt thereof: wherein

R_1 and R_2 are each independently selected from hydrogen; straight or branched chain alkyl of 1 to 15 carbon atoms; cycloalkyl having 3 to 8 carbon atoms optionally substituted by one or more alkyl of 1 to 6 carbon atoms; bicycloalkyl having 3 to 8 carbon atoms in each ring; pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl and tetrahydrothienyl which can be optionally substituted by alkyl of 1 to 6 carbon atoms; pyridyl which can be optionally substituted by alkyl of 1 to 6 carbon atoms; phenyl optionally substituted by one or more groups independently selected from alkyl of 1 to 6 carbon atoms or halogen; straight or branched alkenyl having 3 to 15 carbon atoms with the proviso that the double bond of the alkenyl group cannot be adjacent to the nitrogen; cycloalkenyl having 5 to 8 carbon atoms with the proviso that the double bond cannot be adjacent to the nitrogen; with the further proviso that R_1 and R_2 cannot both be hydrogen

Y is phenyl or phenyl substituted one or more times at one or more of the 2, 3, 5 or 6 positions of the phenyl ring by

substituents independently selected from the group consisting of alkoxy wherein the alkyl is 1 to 6 carbon atoms; halogen wherein the halogen is selected from bromo, fluoro, or chloro; straight or branched chain alkyl having 1 to 6 carbon atoms optionally substituted by one or more halogen atoms; alkylthio wherein the alkyl is 1 to 6 carbon atoms; alkoxyalkyl wherein the alkyl groups are each 1 to 6 carbon atoms; hydroxyalkyl wherein the alkyl is 1 to 6 carbon atoms; alkylthioalkyl wherein the alkyl groups are each 1 to 6 carbon atoms; cyano; mercaptoalkyl wherein the alkyl is 1 to 6 carbon atoms; hydroxy; amino; alkylamino wherein the alkyl group is 1 to 6 carbon atoms; and dialkylamino wherein the alkyl groups are each 1 to 6 carbon atoms,

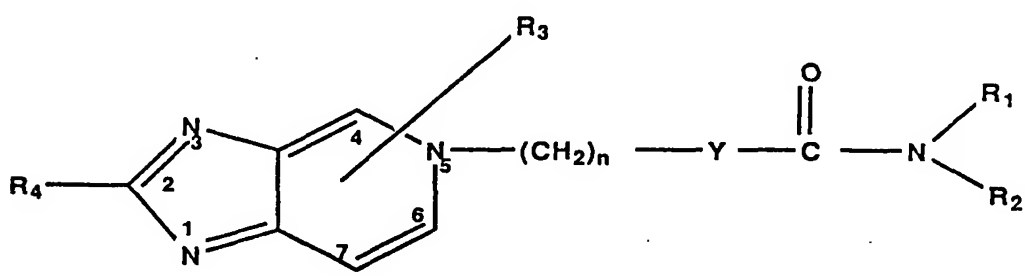
n is an integer of 1 to 5;

R_3 is a group substituted at one or more of the 4, 6, or 7 positions of the pyridine ring said group being independently selected from hydrogen; alkyl of 1 to 6 carbon atoms; halogen wherein the halogen is selected from bromo, fluoro or chloro; and alkoxy wherein the alkyl is 1 to 6 carbon atoms; and

R_4 is hydrogen or alkyl of 1 to 6 carbon atoms.

The invention further relates to pharmaceutical compositions comprising a compound of formula I. Such compounds and compositions have potent and specific PAF antagonistic activities and are thereby useful in the treatment of various diseases or disorders mediated by PAF, for example inflammation, cardiovascular disorders, asthma, lung edema, and adult respiratory distress syndrome.

A preferred embodiment of the present invention are compounds of the formula



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or a pharmaceutically acceptable acid addition salt thereof; wherein

R_1 and R_2 are each independently selected from hydrogen; straight or branched chain alkyl of 1 to 15 carbon atoms; cycloalkyl having 3 to 8 carbon atoms optionally substituted by one or more alkyl of 1 to 6 carbon atoms; bicycloalkyl having 3 to 8 carbon atoms in each ring; phenyl optionally substituted by one or more groups independently selected from alkyl of 1 to 6 carbon atoms or halogen; straight or branched alkenyl having 3 to 15 carbon atoms with the proviso that the double bond of the alkenyl group cannot be adjacent to the nitrogen; cycloalkenyl having 5 to 8 carbon atoms with the proviso that the double bond cannot be adjacent to the nitrogen; with the further proviso that R_1 and R_2 cannot both be hydrogen;

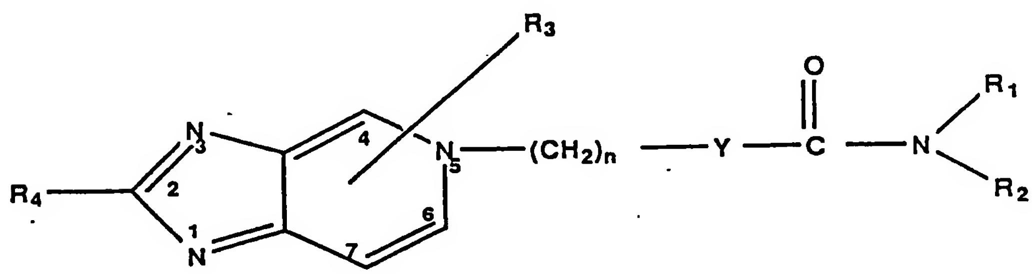
Y is phenyl or phenyl substituted one or more times at one or more of the 2, 3, 5 or 6 positions of the phenyl ring by substituents independently selected from the group consisting of alkoxy wherein the alkyl is 1 to 6 carbon atoms; halogen wherein the halogen is selected from bromo, fluoro, or chloro; straight or branched chain alkyl having 1 to 6 carbon atoms; straight or branched chain alkyl substituted one or more times by halogen;

n is an integer of 1 to 5;

R_3 is a group substituted at one or more of the 4, 6, or 7 positions of the pyridine ring said group being independently selected from hydrogen; alkyl of 1 to 6 carbon atoms; and

R_4 is hydrogen or alkyl of 1 to 6 carbon atoms.

A further embodiment of the present invention are compounds of the formula



I

or a pharmaceutically acceptable acid addition salt thereof; wherein

R_1 and R_2 are each independently selected from hydrogen; straight or branched chain alkyl of 1 to 15 carbon atoms; cycloalkyl having 3 to 8 carbon atoms optionally substituted by one or more alkyl of 1 to 6 carbon atoms; phenyl optionally substituted by one or more groups independently selected from alkyl of 1 to 6 carbon atoms or halogen; R_1 and R_2 cannot both be hydrogen;

Y is phenyl or phenyl substituted one or more times at one or more of the 2, 3, 5 or 6 positions of the phenyl ring by substituents independently selected from the group consisting of alkoxy wherein the alkyl is 1 to 6 carbon atoms; halogen wherein the halogen is selected from bromo, fluoro, or chloro; straight or branched chain alkyl having 1 to 6 carbon atoms;

n is an integer of 1 to 5;

R_3 is a group substituted at one or more of the 4, 6, or 7 positions of the pyridine ring said group being independently selected from hydrogen; and alkyl of 1 to 6 carbon atoms; and

R_4 is hydrogen or alkyl of 1 to 6 carbon atoms.

As used herein the term "alkyl of 1 to 15 carbon atoms" refers to straight chain or branched chain saturated hydrocarbon groups having from one to fifteen carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl, isohexyl, octyl, decyl and the like.

As used herein the term "cycloalkyl having 3 to 8 carbon atoms" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclo-hexyl, cycloheptyl, cyclooctyl.

As used herein the term halogen includes fluoro, chloro and bromo.

As used herein the term "alkenyl having 3 to 15 carbon atoms" refers to straight or branched unsaturated hydrocarbon groups having from 3 to 15 carbon atoms. Illustrative of such alkenyl groups are 2-propenyl, hexenyl, octenyl, decenyl and the like.

As used herein the term "alkoxy wherein the alkyl is 1 to 6 carbon atoms" refers to straight or branched chain ethers. Illustrative of such groups are methoxy, ethoxy, propoxy, butoxy, isopropoxy and the like.

The term "hydroxyalkyl" refers to straight or branched alkyl group having one to six atoms any one of which may be substituted with one or more hydroxyl group.

The term "alkylthio" refers to straight or branched thio-containing radicals, respectively having an alkyl group of one to six carbon atoms attached.

The term "mercaptoalkyl" refers to a terminal mercapto group attached to an alkyl portion of one to six carbon atoms which can be straight or branched.

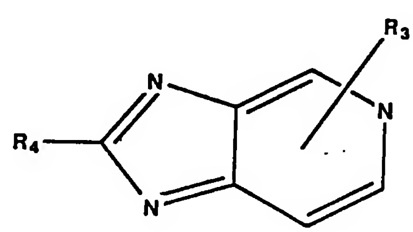
Included within the embodiments of the present invention are the tautomeric forms of the described compounds, isomeric forms including geometric isomers, enantiomers and diastereoisomers, and the pharmaceutically acceptable salts thereof.

The term "pharmaceutically acceptable acid addition salt" refers to a salt prepared by contacting a compound of formula (I) with an acid whose anion is generally considered suitable for human consumption. Examples of pharmacologically acceptable acid addition salts include the hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate, malate, succinate, and tartrate salts. All of these salts may be prepared by conventional means by reacting, for example, the appropriate acid with the corresponding compound of Formula I.

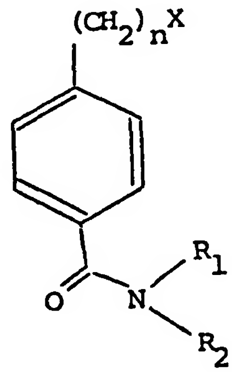
The compounds of formula (I) may be prepared in accordance with the following procedures.

Imidazopyridine which is represented by the following formula

II



wherein R_3 and R_4 are defined as before is reacted with a haloalkylbenzamide which is represented by the following formula



III

wherein R_1 and R_2 and n are defined as before and X is chloro, bromo, or methanesulfonyloxy to give the compounds of formula I. It is understood that the haloalkylbenzamide can also be substituted by halogen, alkyl of 1 to 6 carbon atoms; alkoxy wherein the alkyl is 1 to 6 carbon atoms; alkylthio wherein the alkyl is 1 to 6 carbon atoms; alkoxy alkyl wherein the alkyl is 1 to 6 carbon atoms; hydroxyalkyl wherein the alkyl is 1 to 6 carbon atoms; alkylthioalkyl wherein the alkyl is 1 to 6 carbon atoms; cyano; mercaptoalkyl wherein the alkyl is 1 to 6 carbon atoms; hydroxy; amino; alkylamino wherein the alkly group are each 1 to 6 carbon atoms and dialkylamino wherein the alkyl group are each 1 to 6 carbon atoms.

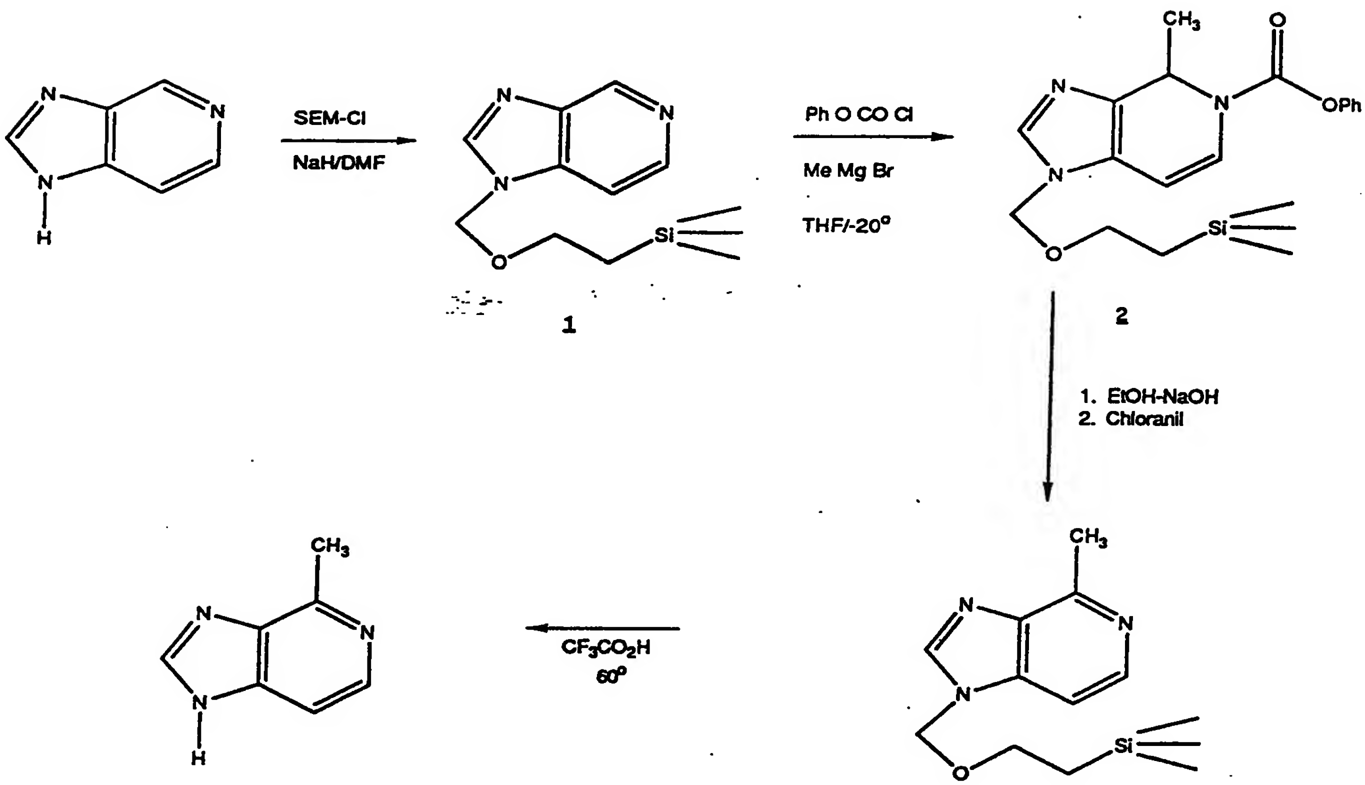
Preferred reaction conditions for the above-identified procedure include heating overnight at 70-90°C a solution of haloalkylbenzamide and imidazopyridine in a solvent such as dimethylacetamide

(approximately 0.1M in each). After heating overnight the reaction solvent is removed in vacuo and the residue diluted with water and basified with ammonium hydroxide. The aqueous solution is extracted with chloroform and the combined organic extracts are backwashed with saturated aqueous sodium chloride solution. The organic solution is dried over sodium sulfate or magnesium sulfate, the drying agent filtered and the filtrate concentrated in vacuo to give the crude product. Purification is effected by chromatography on silica gel using mixtures of chloroform, ethanol and ammonium hydroxide.

A preferred work up for the above-described procedure is to cool the reaction solution which had been heated overnight to room temperature and remove the solvent under reduced pressure at <45°C. The residue obtained is triturated with excess of dry ether and filtered. The crude product is purified by chromatography.

Preparation of Intermediates

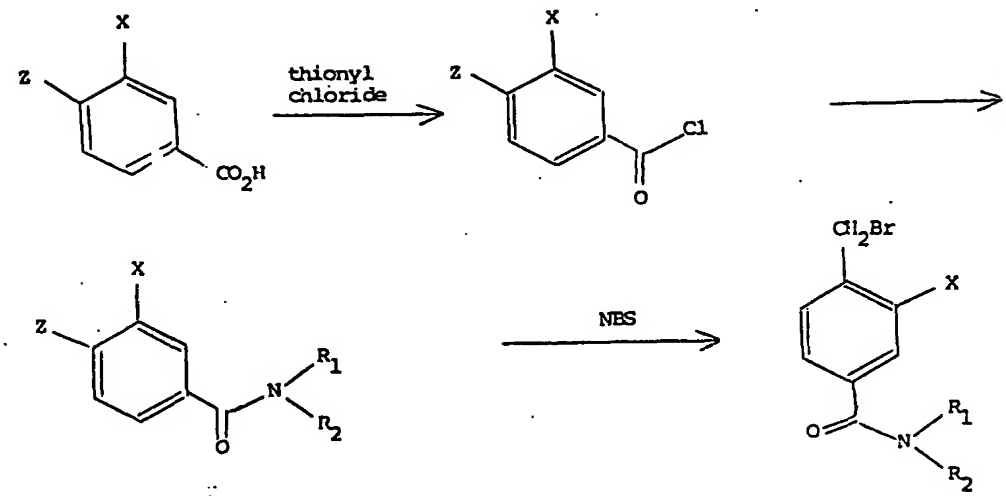
SCHEME A



The imidazo [4,5-c]pyridine wherein R_3 is 4-methyl is prepared according to the scheme above starting with the imidazopyridine of Formula II. Position 1 of this compound is protected by reaction with a 2-(trialkylsilyl) ethoxy methyl chloride and a base such as sodium hydride or potassium hydride in a polar aprotic solvent such as dimethylformamide. This reaction is carried out at room temperature. A specific example of such a protecting reagent is 2-(trimethylsilyl)ethoxymethyl chloride. The protected imidazopyridine is reacted with phenyl chloroformate and methylmagnesium bromide in an ether solvent such as tetrahydrofuran at about -20°C. The methylated product bearing phenoxycarbonyl at position 5 is treated with a base, such as alcoholic sodium hydroxide, at reflux for 24 hr. The product is oxidized with, for example, chloranil, and the 2-(trimethylsilyl)ethoxymethyl group is removed by treatment with a suitable acid. An example of such an acid would be trifluoroacetic acid. Preparation of the unsubstituted imidazo [4,5-c] pyridine is described in U. S. Patent No. 4,804,658.

The haloalkyl benzamides are prepared according to the following reaction scheme

Scheme B



wherein R_1 and R_2 are defined as before; Z is CH_2Br or H; X is fluoro, OMe or methyl

Thus according to the above scheme the acid chlorides were prepared from the corresponding carboxylic acids by refluxing in thionyl chloride (2 molar excess) for two hours. Excess thionyl chloride was removed by azeotrope with toluene. The residual acid chloride was dissolved in THF and cooled to -10°C. A solution of two molar equivalents of the secondary amine in the THF was added dropwise with stirring. When addition was completed, the reaction was allowed to warm to room temperature and stirred for 1-2 hours. The reaction was quenched with 1N HCl diluted with H_2O and extracted three times with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, with water and with saturated aqueous sodium chloride and dried

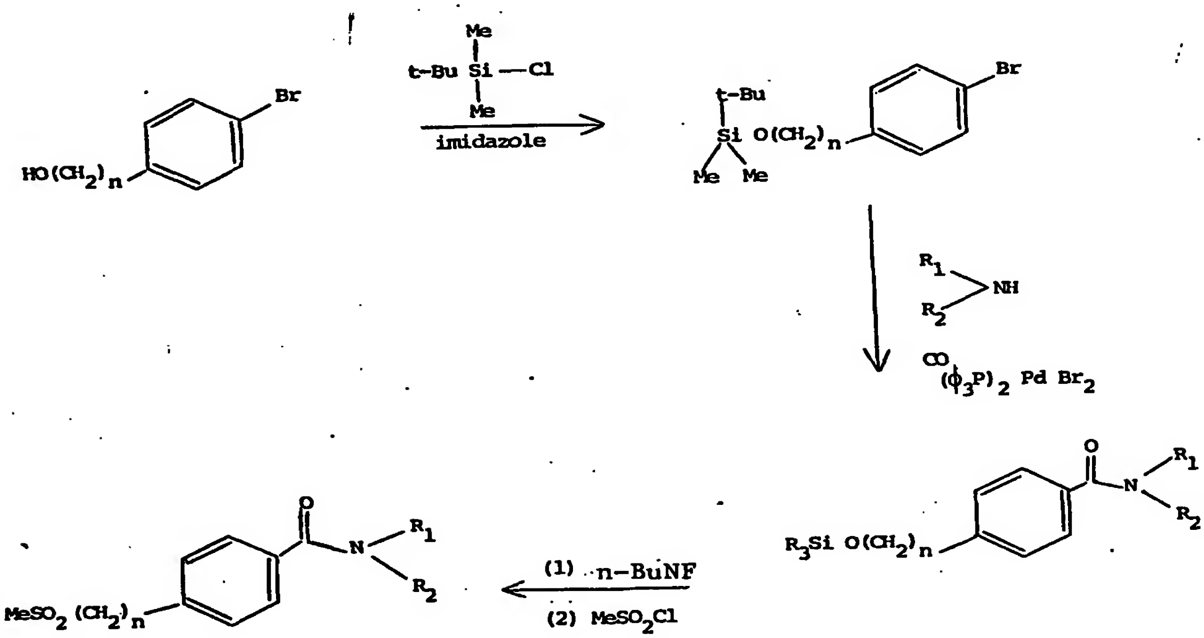
over sodium sulfate. The drying agent was filtered and the filtrate concentrated in vacuo to give a crude product that was chromatographed on silica gel using mixtures of ethyl acetate and hexane to give the purified amide.

When Z = CH_2Br and X = H, the above description is sufficient for the preparation of the compounds of Formula III. When Z = CH_3, and X = OMe or F, or when Z = H and X = CH_3 then compound of Formula VI must be treated with a halogenating agent such as N-bromo succinimide.

A stirred mixture of the purified amide and NBS (1:1 molar ratio) in carbon tetrachloride was irradiated with a sun lamp for 1-3 hours. A white precipitate was filtered and washed with a minimum amount of $CHCl_3$. The filtrate was washed with water and the aqueous layer, after basification with ammonium hydroxide, was extracted three times with chloroform. All organic layers were combined, washed three times with saturated aqueous sodium chloride solution and dried over sodium sulfate.

The drying agent was filtered and the filtrate concentrated in vacuo to give a crude product that was chromatographed on silica gel using mixtures of ethyl acetate and hexane to give the purified bromomethyl compound.

Scheme C



The benzamides wherein n = 2 or 3 can be prepared according to the scheme above starting with the appropriate hydroxyalkyl bromobenzene. The hydroxyl group was protected as a trialkylsilyl ether by reaction with a trialkylsilyl chloride and imidazole in a suitable solvent such as dimethylformamide. An example of such a protecting group would be the t-butyldimethylsilyl ether. The crude silyl ether was purified by chromatography on silica gel using mixtures of ethyl acetate and hexane. The aryl bromide was converted to the carboxamide according to the procedure of Schoenberg et al. [J. Org. Chem., 39, 3327(1974)]. Thus, the aryl bromide was reacted with carbon monoxide in the secondary amine as

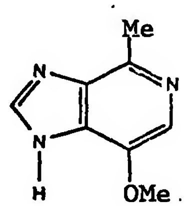
solvent using bistriphenylphosphine palladium(II) dibromide as catalyst at about 100°C for 8-26 hr. in a pressure vessel. The reaction vessel was vented, the reaction mixture triturated with ethyl ether and the washings filtered. The filtrate was washed with 10% aqueous HCl, water and brine. After drying over a suitable drying agent, such as magnesium sulfate, and filtering, the filtrate was concentrated and the residue chromatographed on silica gel using mixtures of ethyl acetate and hexane as eluent to give pure product. The silyl ether was removed by reaction with tetra-n-butylammonium fluoride and the alcohol was converted to a sulfonate ester by reaction with an alkyl or arylsulfonyl chloride. An example of such a sulfonate would be the methanesulfonate.

The secondary amines may be prepared by any number of methods known to those skilled in the art. See references

- Emerson, W. S. Org. Reactions 4, 174 1948)
- J. B. Cambell, L. B. Lavaginino in "Catalysis in Organic Synthesis" (Jones W. H., ed.) p. 43, Academic Press, New York, 1980.

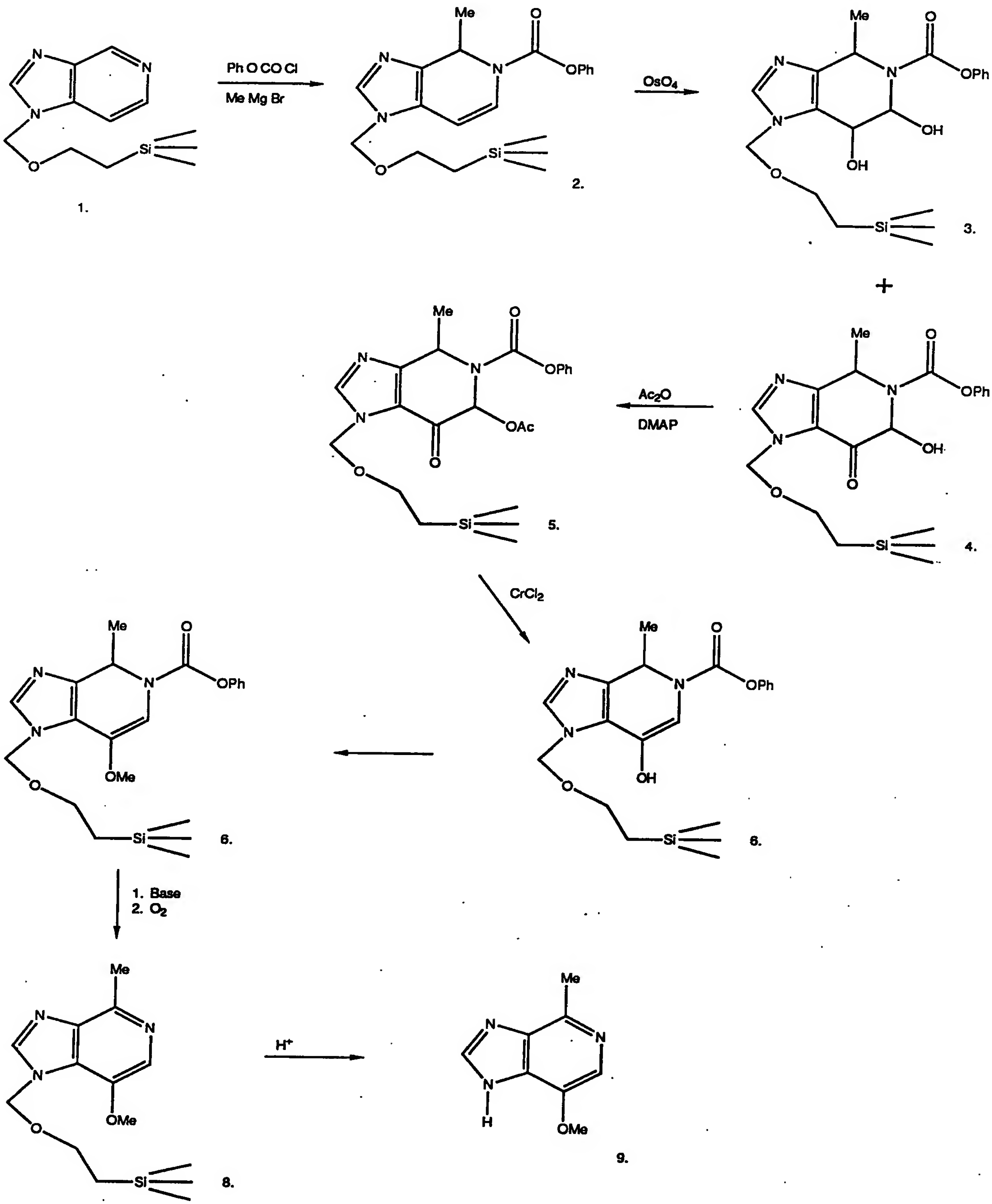
Preparation of

4-Methyl-7-methoxy-imidazopyridine



The above-mentioned compound can be prepared by the following:

SCHEME D

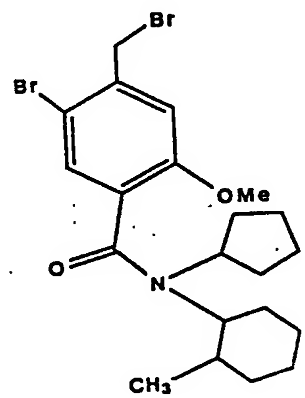


Thus the addition product 2 which is isolated on reacting 1 with phenyl chloroformate and methyl magnesium bromide is treated with osmium tetroxide in aqueous acetone containing N-methylmorpholine-N-oxide at room temperature for 24 hours to give the diol 3 and the hydroxyketone 4. The hydroxyketone 4 is acetylated (acetic anhydride, DMAP methylene chloride, room temperature, 24 hrs) and treated

with $CrCl_2$ in acetone to give the deacetoxylated product 6. Product 6 is treated with NaH in DMF and then with iodomethane to give the methyl ether 7. Cleavage of carbamate and oxidation gives the N-1 protected 4-methyl-7-methoxy imidazopyridine product 8. Deprotection of product 8 gives the 4-methyl-7-methoxy-imidazo-pyridine.

Preparation of

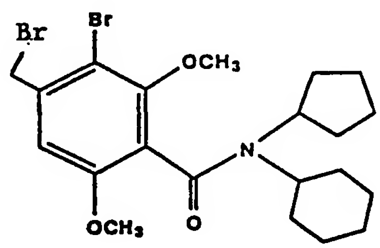
2-Methoxy-4-bromomethyl-5-bromo-N-cyclopentyl-N-(2-methylcyclohexyl)benzamide



The above compound is prepared from 2-methoxy-4-methyl-N-cyclopentyl-N-(2-methylcyclohexyl)benzamide and N-bromo succinimide in carbon tetrachloride by irradiation with a sun lamp for 5 hours.

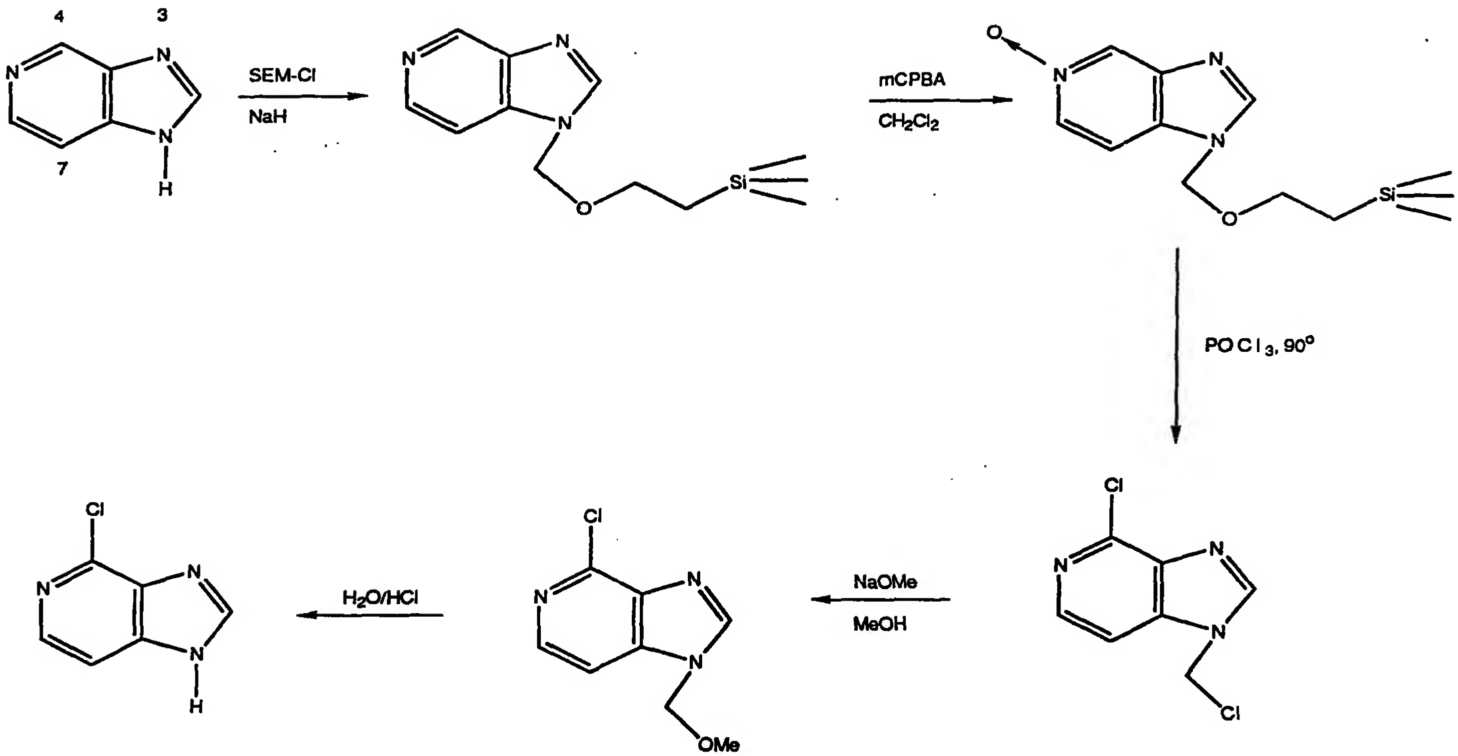
Preparation of

2,6-Dimethoxy-3-bromo-4-bromomethyl
(N-cyclohexyl-N-cyclopentyl)benzamide



The above compound is prepared from 2,6-dimethoxy-4-methyl benzoic acid described by I.W. Mathison, R.C. Gueldner, D.M. Carroll, J. Pharma Sci 57 1820 (1968). The substituted benzoic acid is converted to the corresponding amide by first converting said compound to the acid chloride (using thionyl chloride) followed by condensation with N-cyclohexyl-N-cyclopentylamine. Irradiation of 2,6-dimethoxy-4-methyl-N-cyclohexyl-N-cyclopentylbenzamide following the procedure described for the preparation 2-methoxy-4-bromomethyl-5-bromo-N-cyclopentyl-N-(2-methylcyclohexyl)benzamide gives two products 2,6-dimethoxy-3-bromo-4-methyl-N-cyclohexyl-N-cyclopentylbenzamide and 2,6-dimethoxy-3-bromo-4-bromomethyl-N-cyclohexyl-N-cyclopentylbenzamide. The second product is the predominating product.

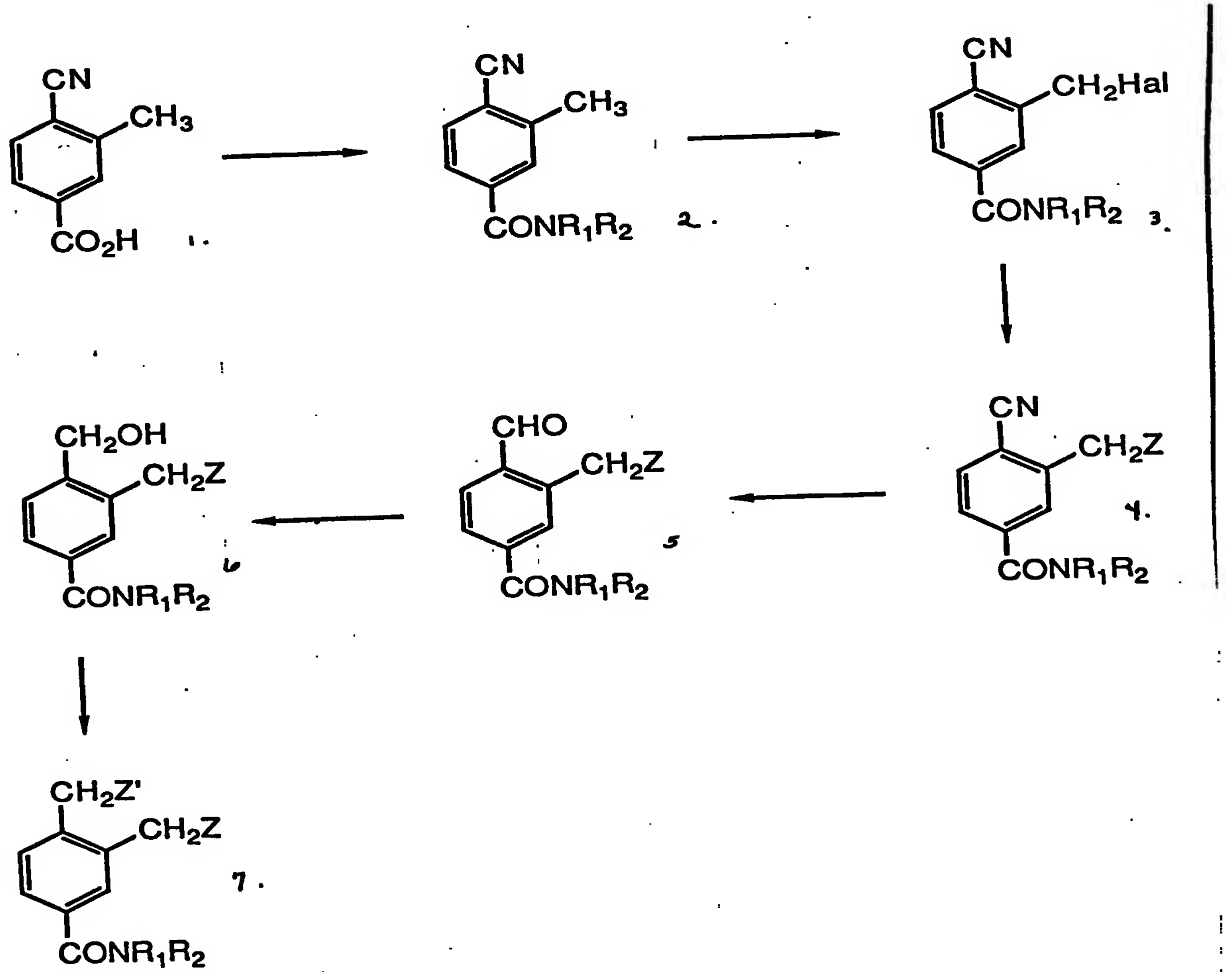
SCHEME E



The imidazo[4,5-c]pyridine wherein R_3 is 4-chloro is prepared according to Scheme E starting with the imidazopyridine of Formula II. Position 1 of this compound is protected by reaction with a 2-(trialklysilyl) ethoxy methyl chloride and a base such as sodium hydride or potassium hydride in a polar aprotic solvent such as dimethylformamide. The reaction is carried out at room temperature. The protected imidazopyridine is reacted with m-chloroperbenzoic acid in methylene chloride at room temperature to give the pridine N-oxide product. The N-oxide product is heated in $POCl_3$ at 90°C to give

4-chloro-1-chloromethyl imidazopyridine. Treatment of this compound with sodium methoxide in methanol gave the 4-chloro-1-methoxy ethyl imidazopyridine. Reacting this compound with water/acid with heating gave the 4-chloro-imidazo[4,5-c] pyridine.

Preparation of Alkoxyalkyls



wherein R_1 and R_2 are defined as before; "Hal" is halogen; Z is alkoxy, alkylthio, mercapto, hydroxy, halo, amino, alkyl and dialkylamino; and Z' chloro, bromo, methanesulfonyloxy or p-toluenesulfonyloxy.

When Y is substituted with alkoxyalkyl, such substitution may be carried out by methods known to those skilled in the art. Such a method might, for example, employ the substituted benzoic acid 1 (F. Fichter, G. Shetty, Helv. Chim. Acts, 20, 563 (1937)) as starting material. This is converted to the amide 2 by first converting acid 1 to the acid chloride by contact with agents such as oxalyl chloride or thionyl chloride and then treating the acid chloride with the desired amine. Amide 2 is converted to halide 3 by treatment with a halogenating agent such as N-bromosuccinimide. Halide 3 is versatile and in addition to serving as an intermediate to alkoxyalkyl compounds, is also an intermediate to alkylthioalkyl, hydroxyalkyl, mercaptoalkyl and alkylaminoalkyl compounds by treatment with the appropriate Z derivative. When halogen is displaced with a metal alkoxide, such as sodium methoxide, the methoxymethyl derivative (4, Z = OMe) is obtained. Conversion of 4 (Z = OMe) to aldehyde 5 (Z = OMe) is effected by controlled reduction with a reducing agent such as diisobutylaluminum hydride, followed by acid hydrolysis. Reduction of aldehyde 5 to alcohol 6 is effected by a second reduction with another reducing agent such as sodium borohydride or lithium tri-t-butoxyaluminum

hydride. Alcohol 6 is converted to a derivative suitable for nucleophilic displacement such as 7 where Z' is a leaving group such as halide or aryl or alkyl sulfonate. Such conversion is effected by treatment of 6 with, for example, p-toluenesulfonyl chloride, methanesulfonyl chloride, or thionyl chloride.

Compounds where Y of formula I is substituted with hydroxy can be made from the corresponding methoxy substituted compounds by treatment with a demethylating reagent such as lithium ethyl mercaptide in a dipolar, aprotic solvent such as dimethylformamide at temperatures ranging from room temperature to 200°.

Accordingly, compound (I) can be used among other things to reduce inflammation, to correct respiratory, cardiovascular, and intravascular alterations or disorders, and to regulate the activation or coagulation of platelets, the pathogenesis of immune complex deposition and smooth muscle contractions.

For the treatment of inflammation, cardiovascular disorder, asthma, or other diseases mediated by PAF, compound (I) may be administered orally, topically,

parenterally, or by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art.

Accordingly, the invention provides a class of novel pharmaceutical compositions comprising one or more compounds of the present invention in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and if desired other active ingredients. The compounds and composition may for example be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage

unit contained in a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of active ingredient from about 1 to 250 mg preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight may be appropriate.

The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred daily dose would be from about 1 to 30 mg/kg body weight.

The dosage regimen for treating an infectious disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the infection; the route of administration; and the particular compound employed and thus may vary widely.

For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of

alkanoic acids, cellulose alkyl ethers, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, gelatin, acacia, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and thus tableted or encapsulated for convenient administration. Alternatively, the compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. Appropriate dosages, in any given instance, of course depend upon the nature and severity of the condition treated, the route of administration, and the species of mammal involved, including its size and any individual idiosyncrasies.

Representative carriers, diluents and adjuvants include for example, water, lactose, gelatin, starches, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, petroleum jelly, etc. The pharmaceutical compositions may be made up in a solid form such as granules, powders or suppositories or in a liquid form such as solutions, suspensions or emulsions. The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional pharmaceutical adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, buffers, etc.

Dosage levels of the order from about 1 mg to about 100 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (from about 50 mg to about 5 gs. per patient per day). For example, inflammation is effectively treated and anti-pyretic and analgesic activity manifested by the administration from about 25 to about 75 mg of the compound per kilogram of body weight per day (about 75 mg to about 3.75 gm per patient per day). Preferably, from about 5 mg to about 50 mg per kilogram of body weight per daily dosage produces highly effective results (about 250 mg to about 2.5 gm per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 5 mg to 95 mg of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 25 mg to about 500 mg of active ingredient.

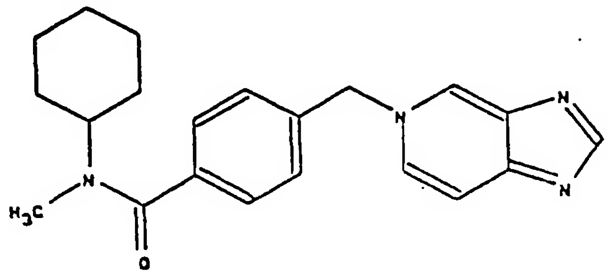
It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of

administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following Examples are intended to further illustrate the present invention and not to limit the invention in spirit or scope. In the Examples, all parts are parts by weight unless otherwise expressly set forth.

EXAMPLE 1

5-[4-(N-methyl-N-cyclohexylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine



To a stirred solution of 5H-imidazo[4,5-c]pyridine (5.86 g, 49.2 mmol) in DMF (125 ml) under a nitrogen atmosphere was added washed, dried sodium hydride (prepared from 3.54 g of 50% dispersion in oil by washing four times with 50-75 ml portions of hexane). After stirring for 1 hr at room temperature, the evolution of hydrogen gas had ceased and the reaction was cooled to 10°C. N-Methyl-N-cyclohexyl-α-bromo-p-toluyl amine (16.9 g, 54.5 mmol) was added. The reaction was stirred at 0° for 45 min. and at room temperature for 3 hrs.

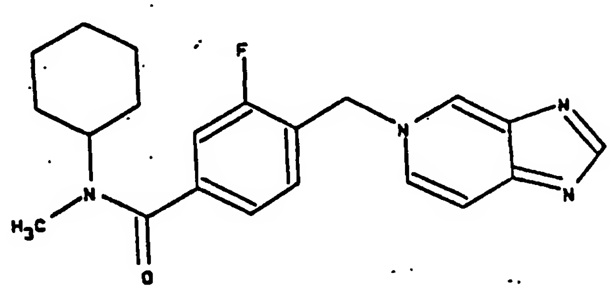
DMF was removed in vacuo and the residue was diluted with H_2O (200 ml) and the resulting solution was saturated with sodium chloride. The aqueous solution was extracted four times with ethyl acetate (100 ml portions) and the combined organic layers were washed three times with saturated aqueous sodium chloride solution (150 ml

portions). After drying over sodium sulfate, the organic solution was filtered and concentrated in vacuo to give 13.38 g of crude product as a brown gum. This material was chromatographed on silica gel using ethanol/chloroform/ammonium hydroxide (20/79/1) to give 3.13 g of compound as an orange oil that crystallized on treatment with ethyl acetate. Recrystallization from ethyl acetate yielded 1.06 g.

Analysis Calcd for $C_{21}H_{24}N_4O$. $1/4H_2O$: C, 71.46; H, 7.00; N, 15.88. Found: C, 71.14; H, 7.18; N, 15.78. m.p. 115-17°C

EXAMPLE 2

5-[4-(N-methyl-N-cyclohexylcarbamoyl)-2-fluorobenzyl]-5H-imidazo[4,5-c]pyridine



A solution of N-methyl-N-cyclohexyl 3-fluoro 4-bromo-methyl benzamide (1.2 g 2.66 mm) and 5H-imidazo-[4,5-c]pyridine (0.48 g 4.0 mm) in dimethylacetamide (25 ml) was heated overnight at 70-80°C with stirring

under N_2. Reaction solvent was removed in vacuo and the residue diluted with water and basified with ammonium hydroxide. The aqueous solution was extracted four times with chloroform and the combined organic extracts were backwashed three times with saturated aqueous sodium chloride solution. The organic solution was dried over magnesium sulfate, the drying agent was filtered and the filtrate concentrated in vacuo to give 0.88 g of the crude compound. Purification of the compound was effected by chromatography on silica using mixtures of chloroform, ethanol and ammonium hydroxide.

Analysis calcd for $C_{21}H_{23}FN_4O$. 0.8 H_2O:

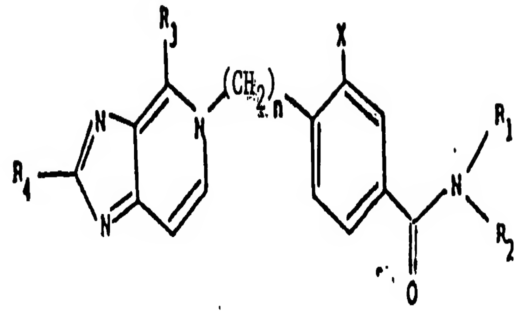
C,66.22; H,6.51; N,14.71; F,4.99.

Found: C,66.03; H,6.44; N,14.65; F,4.91.

mp 154-158°C

In the same manner as described in Example 2 the compounds of the Examples 3 to 11 described in Tables A & B were prepared.

TABLE A



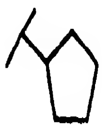
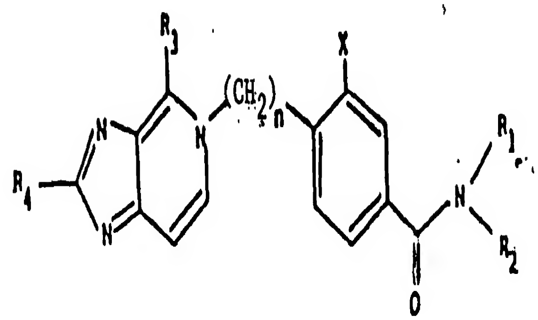
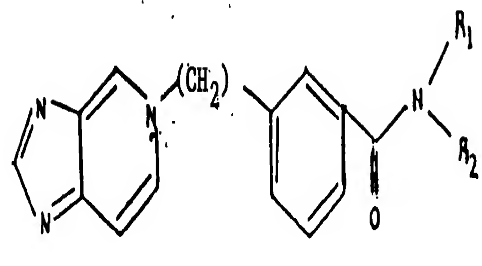
Example	R_1	R_2	X	n	R_3	R_4	M pt (°C)	Analysis Calcd.	Found	Molecular Formula
3			OCH_3	1	H	H	217-19	C 71.12 H 7.26 N 13.28	70.83 7.33 13.06	$C_{25}H_{30}N_4O_2$
4			OCH_3	1	H	H	197-99	C 71.01 H 7.52 N 12.74	70.87 7.49 12.70	$C_{26}H_{32}N_4O_2$ $0.4H_2O$
5			OCH_3	1	H	H	192-95	C 70.90 H 7.44 N 13.78	70.75 7.47 13.71	$C_{24}H_{30}N_4O_2$
6		CH_3	OCH_3	1	H	H	206-08	C 69.15 H 6.86 N 14.67	68.78 6.88 14.57	$C_{22}H_{26}N_4O_2$ $0.2H_2O$

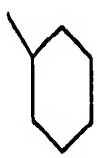
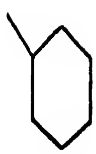
TABLE A (continued)



Example	R_1	R_2	X	n	R_3	R_4	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
7			F	1	H	H	205-08	C 71.14	71.11	$C_{25}H_{29}FN_4O$
								H 6.95	7.11	
								N 13.33	13.16	
								F 4.52	4.30	
8			F	1	H	H	178-82	C 68.46	68.46	$C_{23}H_{27}FN_4O$
								H 6.79	6.71	
								N 13.89	13.45	$0.5H_2O$
								F 4.71	4.38	
9		CH_3	F	1	H	H	154-8	C 66.22	66.03	$C_{21}H_{23}N_4FO$
								H 6.51	6.44	
								N 14.71	14.65	$0.8H_2O$
								F 4.99	4.91	

TABLE B



Example	R_1	R_2	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
10		$-CH_3$	167-69	C 72.38 H 6.94 N 16.08	72.26 7.10 16.01	$C_{21}H_{24}N_4O$
11			209-12	C 73.37 H 7.50 N 14.88	72.97 7.63 14.61	$C_{23}H_{28}N_4O$

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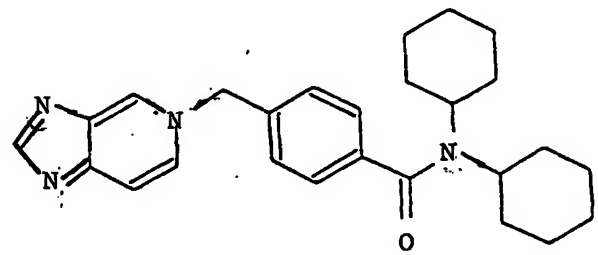
EXAMPLE 12

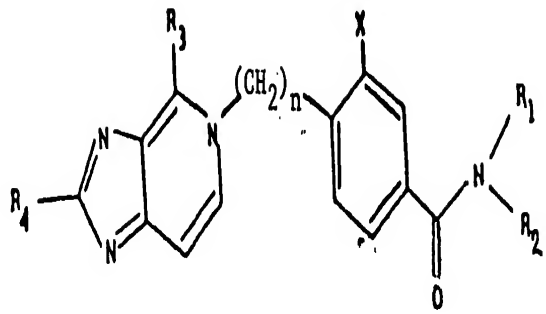
5-[(4-(N,N-dicyclohexylcarbamoyl)benzyl]-5H-imidazo-[4,5c]pyridine



To a stirred solution of 5H-imidazo[4,5-c]pyridine (750 mg, 6.3 mmol) in N,N-dimethylacetamide, 4-bromomethyl-N-N-dicyclohexyl benzamide (2.6 g, 6.88 mmol) was added. The reaction mixture was stirred under argon at 80-85°C. After 24h, the reaction flask was cooled to room temperature and the solvent removed under reduced pressure at < 45°C. The residue obtained was triturated with ether (2 X 70 mL) and filtered. The crude residue (2.7 g) was chromatographed (silica gel, CH_2Cl_2-MeOH-NH_4OH 80-20-1) to give pure product (1.47 g, 62%) which was recrystallized from EtOAc-CH_3CN. mp 233-35°C; Analysis calcd. for $C_{26}H_{32}N_4O$. $0.3H_2O$: C, 74.0: H, 7.73: N, 13.28. Found C, 73.93; H, 7.90; N, 13.09.

In the same manner as described in Example 12 the compounds of the Examples 13 to 38 described in Table C were prepared.

TABLE C



Example	R_1	R_2	X	n	R_3	R_4	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
13		CH_3	H	1	H	H	115-17	C 71.46 H 7.00 N 15.88	71.14 7.18 15.78	$C_{21}H_{24}N_4O$ $0.25H_2O$
14	$\vdash(CH_2)_7CH_3$	H	H	1	H	H	113-15	C 72.52 H 7.69 N 15.38	72.26 7.72 15.28	$C_{22}H_{28}N_4O$
15	$\vdash(CH_2)_9CH_3$	H	H	1	H	H	141-45	C 73.46 H 8.16 N 14.28	73.35 8.32 14.26	$C_{24}H_{32}N_4O$

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TABLE C (continued)

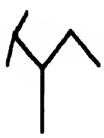
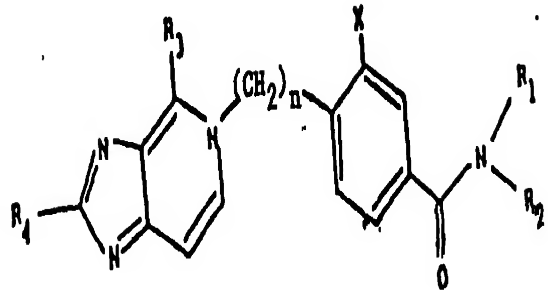
Example	R_1	R_2	X	n	R_3	R_4	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
16			H	1	H	H	209-10	C 72.70 H 7.48 N 14.75	72.92 7.60 14.82	$C_{23}H_{28}N_4O$ $0.2H_2O$
17			H	1	H	H	210-11	C 73.80 H 7.69 N 14.35	73.40 7.78 14.25	$C_{24}H_{30}N_4O$

TABLE C (continued)



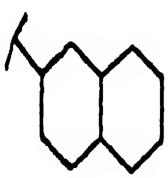
Example	R_1	R_2	X	n	R_3	R_4	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
18	$-(CH_2)_{11}CH_3$	H	H	1	H	H	150-2	C 74.28 H 8.57 N 13.33	74.10 8.75 13.36	$C_{26}H_{36}N_4O$
19		H	H	1	H	CH_3	113-28	C 73.31 H 7.52 N 13.68	73.41 7.79 13.38	$C_{25}H_{30}N_4O$ $0.4H_2O$
20		H	H	1	H	H	221-2	C 72.52 H 7.69 N 15.38	72.33 7.82 15.28	$C_{22}H_{28}N_4O$

TABLE C (continued)

Example	R_1	R_2	X	n	R_3	R_4	M pt (°C)	Analysis Calcd.	Found	Molecular Formula
21		CH_3	H	2	H	H	223-5	C 71.15 H 7.27 N 15.09	70.79 7.48 14.81	$C_{22}H_{26}N_4O$ $0.6H_2O$
22		CH_3	H	3	H	H		C 70.86 H 7.57 N 14.36	70.82 7.64 14.23	$C_{23}H_{28}N_4O$ $0.75H_2O$
23			H	1	H	CH_3	197-98	C 74.62 H 7.46 N 13.93	74.24 7.50 13.80	$C_{25}H_{30}N_4O$
24			H	1	CH_3	H	225-8	C 72.31 H 7.48 N 13.18	72.36 7.87 13.50	$C_{25}H_{30}N_4O$ $0.7H_2O$

TABLE C (continued)

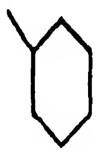
Example	R_1	R_2	X	n	R_3	R_4	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
25			H	1	H	H	190-3	C 74.22 H 7.21 N 14.43	73.98 7.27 14.33	$C_{24}H_{28}N_4O$
26			H	1	H	H	222-23	C 74.62 H 7.46 N 13.93	74.21 7.45 14.26	$C_{25}H_{30}N_4O$
27			H	1	H	H	233-35	C 74.0 H 7.73 N 13.28	73.93 7.90 13.07	$C_{26}H_{32}N_4O$ $0.5H_2O$
28			H	1	H	H	197-98	C 73.84 H 7.69 N 14.35	73.86 7.87 14.36	$C_{24}H_{30}N_4O$

TABLE C (continued)

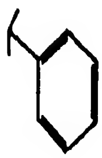
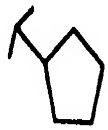
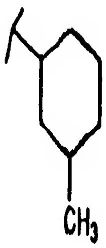
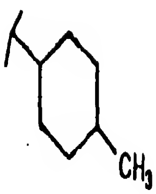
Example	R_1	R_2	X	n	R_3	R_4	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
29			H	1	H	H	213-14	C 75.73 H 6.10 N 14.13	75.66 6.18 14.08	$C_{25}H_{24}N_4O$
30			H	1	H	H	187-89	C 74.94 H 7.74 N 13.44	74.58 7.84 13.32	$C_{26}H_{32}N_4O$
31			H	1	H	H	211-12	C 74.94 H 7.74 N 13.44	74.85 7.84 13.39	$C_{26}H_{32}N_4O$

TABLE C (continued)

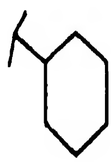
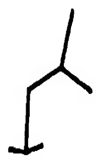
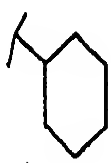
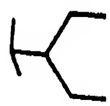
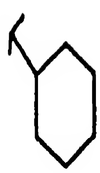
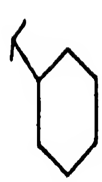
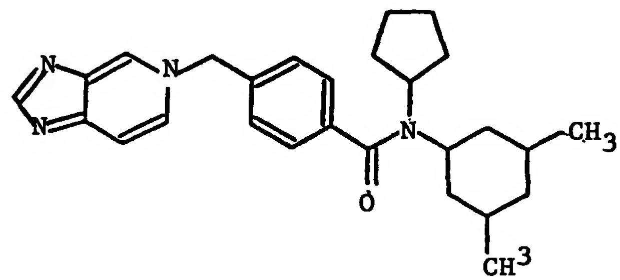
Example	R_1	R_2	X	n	R_3	R_4	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
32			H	1	H	H	198-200	C 73.84 H 7.69 N 14.35	73.20 7.70 14.74	$C_{24}H_{30}N_4O$
33			H	1	H	H	211-13	C 73.60 H 7.85 N 13.73	73.72 7.92 13.72	$C_{25}H_{32}N_4O$ $0.2H_2O$
34			H	1	H	H	88-90	C 72.06 H 7.04 N 14.62	72.25 7.16 14.48	$C_{23}H_{26}N_4O$ $0.5H_2O$

TABLE C (continued)

Example	R_1	R_2	X	n	R_3	R_4	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
35			H	1	H	H	224-5	C 71.42 H 7.14 N 16.66	71.30 7.29 16.71	$C_{20}H_{24}N_4O$
36			H	1	H	H	228-30	C 74.22 H 7.21 N 14.43	74.04 7.29 14.28	$C_{24}H_{28}N_4O$
37		H	H	1	H	H	219-21	C 70.33 H 6.68 N 16.41	70.34 6.87 16.28	$C_{20}H_{22}N_4O$ $0.4H_2O$
38		$-CH_2CH_3$	H	1	H	H	156-8	C 71.85 H 7.24 N 15.24	71.85 7.24 15.19	$C_{22}H_{26}N_4O$ $0.3H_2O$

EXAMPLE 39

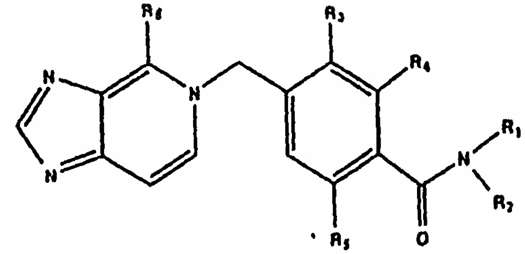
Preparation of
5-[4{-[N-cyclopentyl-N-(3,5-dimethylcyclohexyl)]-carbamoyl}benzyl]-5H-imidazo[4,5-c]pyridine



To a stirred solution of 5H-imidazo[4,5-c]pyridine (400 mg, 3.4 mmol) in N,N-dimethylacetamide (30 ml), 4-bromomethyl-N-cyclopentyl-N-(3,5-dimethylcyclohexyl) benzamide (1.4 g, 3.57 mmol) was added. The reaction mixture was stirred under argon at 80-85°C. After 4h, the reaction flask was cooled to room temperature and the solvent removed under reduced pressure at <45°C. The residue obtained was triturated with ether (2x70 ml) and filtered. The crude residue (1.8g) was chromatographed (silica gel, CH_2Cl_2-MeOH-NH_4OH 90-10-1) to give pure product (1.05 g, 72%) which was recrystallized from EtOAc-CH_3CN. mp 214-16°C.
Anal calcd. for $C_{27}H_{34}N_4O$: C, 75.30; H, 7.9; N, 13.02.
Found: C, 74.92; H, 8.07; N, 12.97.

In the same manner as described in Example 39 the compounds of the Examples 40 to 55 described in Table D were prepared.

Table D



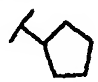
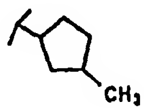
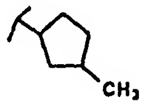
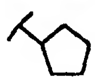
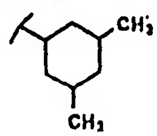
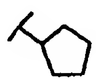
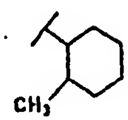
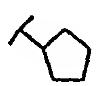
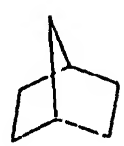
Example	R_1	R_2	R_3	R_4	R_5	R_6	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
40			H	H	H	H	204-6	C 74.62 H 7.46 N 13.93	74.12 7.56 13.90	$C_{25}H_{30}N_4O$
41			H	H	H	H	229-31	C 73.40 H 7.45 N 14.89	73.13 7.64 14.85	$C_{23}H_{28}N_4O$
42			H	H	H	H	214-16	C 75.30 H 7.90 N 13.02	74.92 8.07 12.97	$C_{27}H_{34}N_4O$
43			H	H	H	H	223-5	C 74.96 H 7.74 N 13.45	74.65 7.79 13.35	$C_{26}H_{32}N_4O$
44			H	H	H	H	182-5	C 75.00 H 7.31 N 13.46	74.72 7.35 13.37	$C_{26}H_{30}N_4O$ $0.1H_2O$

Table D (cont'd.)

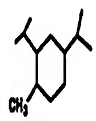
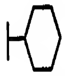
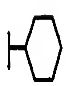
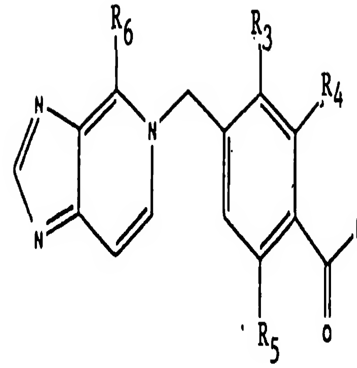
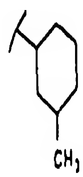
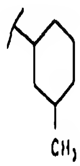
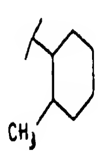
Example	R_1	R_2	R_3	R_4	R_5	R_6	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
45	H		H	H	H	H	242-4	C 66.79 H 5.26 N 19.47	66.79 4.97 19.26	$C_{20}H_{17}N_5O$ $0.9H_2O$
46			H	H	H	H	95-103	C 73.76 H 8.43 N 11.86	73.83 8.25 11.65	$C_{29}H_{38}N_4O$ $0.75H_2O$
47			OCH_3	H	H	OH	235-37	C 68.22 H 7.15 N 13.26	67.86 7.23 13.09	$C_{24}H_{30}N_4O_3$
48			OCH_3	H	H	Cl	171-3	C 65.32 H 6.62 N 12.70 Cl 8.10	64.96 6.78 12.51 8.47	$C_{24}H_{29}N_4O_2Cl$
49			OCH_3	H	H	OCH_3	212-14	C 66.71 H 7.50 N 12.40	66.53 7.25 12.26	$C_{25}H_{32}N_4O_3$ $0.75H_2O$

TABLE D (continued)

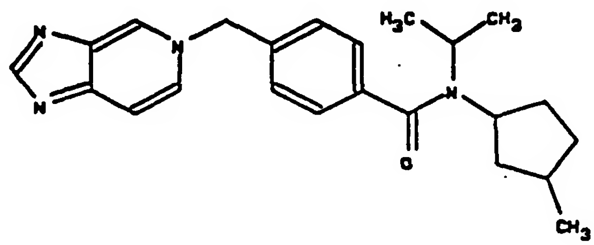


Example	R_1	R_2	R_3	R_4	R_5	R_6	M pt (°C)	Analysis Calcd.	Analysis Found	Molecular Formula
50			H	OCH_3	H	H	226-8	C 72.60 H 7.67 N 12.54	72.28 7.65 12.44	$C_{27}H_{34}N_4O_2$
51			OCH_3	H	H	H	186-8	C 72.60 H 7.67 N 12.54	72.21 7.91 12.28	$C_{27}H_{34}N_4O_2$
52			OCH_3	OCH_3	H	H	214-16	C 69.29 H 7.45 N 11.97	69.01 7.42 11.86	$C_{27}H_{34}N_4O_3$ $0.3H_2O$
53			Br	OCH_3	OCH_3	H	191-3	C 57.95 H 6.30 N 10.01 Br 14.3	57.56 6.01 9.93 15.8	$C_{27}H_{33}N_4O_3Br$ $1H_2O$
54			Br	H	OCH_3	H	167-70	C 60.67 H 6.41 N 10.48 Br 14.95	60.47 6.24 10.00 14.57	$C_{27}H_{35}N_4O_2Br$ $0.5H_2O$
55			OMe	H	H	H	210-13	C 64.41 H 7.09 N 12.52 Cl 7.92	64.40 7.34 12.43 8.0	$C_{24}H_{30}N_4O_2$ $0.25H_2O$

EXAMPLE 56

Preparation of

5-[4{-[N-isopropyl-N-(3-methylcyclopentyl)]carbamoyl}benzyl]-5H-imidazo[4,5-c]pyridine

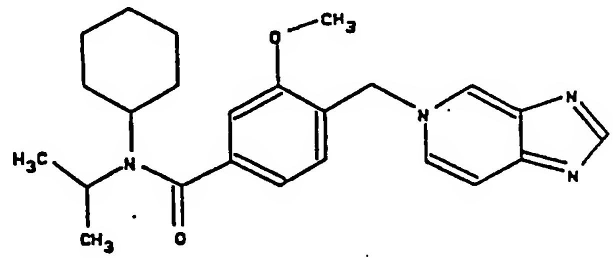


To a stirred solution of 5H-imidazo[4,5-c]pyridine (689 mg, 5.76 mmol) in N,N-dimethylacetamide (30 ml), 4-bromomethyl-N-isopropyl-N-(3-methylcyclohexyl)benzamide (2.17 g, 6.42 mmol) was added. The reaction mixture was stirred under argon at 95°C. After 48h, the reaction flask ws cooled to room temperature and the solvent removed under reduced pressure at <45°C. The residue obtained was triturated with ether (2x100ml) and filtered. The crude residue (2.97g) was chromatographed (silica gel, CH_2Cl_2-MeOH-NH_4OH 90-10-1) to give pure product (.93g, 43%) which was recrystallized from EtOAc-CH_3CN. mp 229-31°C. Anal calcd. for $C_{23}H_{28}N_4O$: C, 73.40; H, 7.45; N, 14.89. Found C, 73.13; H, 7.64; N, 14.85.

EXAMPLE 57

Preparation of

5-[4-(N-isopropyl-N-cyclohexylcarbamoyl)-2-methoxy-benzyl]-5H-imidazo[4,5-c]pyridine

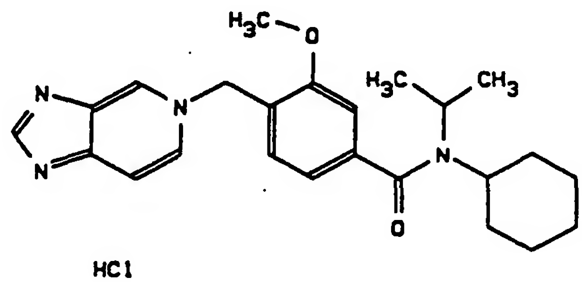


To a stirred solution of 5H-imidazo[4,5-c]pyridine (1.5g, 12.6 mmol) in dimethylacetamide (120 ml) under argon, N-isopropyl-N-cyclohexyl-3-methoxy-4-bromomethylbenzamide (5.1 g, 13.86 mmol) was added in one portion. The reaction temperature was slowly raised to 80-85°C and was stirred over the week-end. The reaction flask was cooled to room temperature and the solvent removed under reduced pressure at <45°C. The residue obtained was triturated with excess of dry ether (2X100 ml) and filtered. The crude product was chromatographed (silica gel; CH_2Cl_2 : MeOH : NH_4OH :: 90 : 10 :1) to give pure alkylated product (3.53 g, 69%). The product could be recrystallized from ethyl acetate. mp 192-95°C. Anal calcd. for $C_{24}H_{30}N_4O_2$: C, 70.90; H, 7.44; N, 13.78. Found C, 70.58; H, 7.43; N, 13.78.

EXAMPLE 58

Preparation of

5-[4-{N-isopropyl-N-cyclohexylcarbamoyl}-2-methoxy-benzyl]-5H-imidazo[4,5-c]pyridine hydrochloride

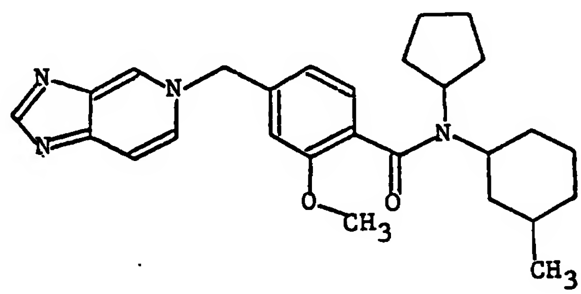


To clear solution of the product of Example 57 (100 mg) in methanol (7 ml), HCl in dioxane (5ml, 6N solution) was added. After stirring at room temp. for 2h, the solvent was removed under reduced pressure. Ethyl acetate (25ml) was added and mixture was refluxed for 1h. The contents were filtered hot and the residue was washed with more hot ethyl acetate. After drying, the product (92mg) was collected, mp 210-13°C. Anal calcd. for $C_{24}H_{31}N_4ClO_2$ $0.25H_2O$: C, 64.41; H, 7.09; N, 12.52; Cl, 7.92. Found C, 64.40; H, 7.34; N, 12.43, Cl, 8.0.

EXAMPLE 59

Preparation of

5-[4-{N-cyclopentyl-N-(3-methylcyclohexyl)carbamoyl}-3-methoxybenzyl]-5H-imidazo[4,5-c]pyridine

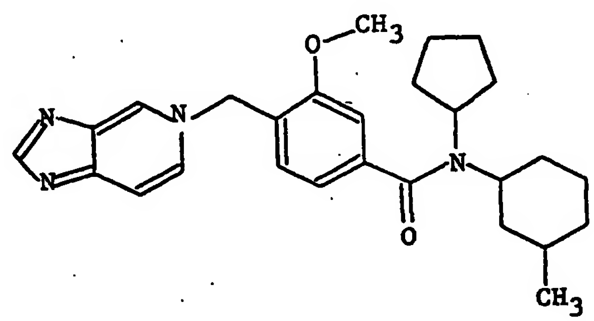


To a stirred solution of 5H-imidazo[4,5-c]pyridine (412mg, 3.47mmol) in N,N-dimethylacetamide (25 ml), 4-bromomethyl-2-methoxy-N-cyclopentyl-N-(3-methylcyclohexyl)benzamide (1.49g, 3.65 mmol) was added. The reaction mixture was stirred under argon at 90–95°C. After 48h, the reaction flask was cooled to room temperature and the solvent removed under reduced pressure at <45°C. The residue obtained was triturated with ether (2X70ml) and filtered. The crude residue (1.85g) was chromatographed (silica gel, CH_2Cl_2-MeOH-NH_4OH 90-10-1) to give pure product (1.05g, 67%) which was recrystallized from EtOAc. mp 226–28°C. Anal calcd. for $C_{27}H_{34}N_4O_2$: C, 72.60; H, 7.67; N, 12.54. Found C, 72.28; H, 7.65; N, 12.44.

EXAMPLE 60

Preparation of

5-[4-(N-cyclopentyl-N-(3-methylcyclohexyl)carbamoyl)-2-methoxybenzyl]-5H-imidazo[4,5-c]pyridine

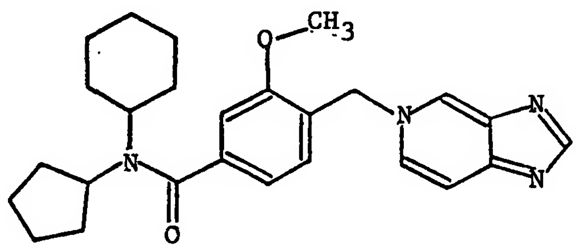


To a stirred solution of 5H-imidazo[4,5-c]pyridine (525mg, 4.4mmol) in N,N-dimethylacetamide (25 ml), 4-bromomethyl-3-methoxy-N-cyclopentyl-N-(3-methylcyclohexyl)benzamide (1.9g, 4.66mmol) was added. The reaction mixture was stirred under argon at 90-95°C. After 48h, the reaction flask was cooled to room temperature and the solvent removed under reduced pressure at <45°C. The residue obtained was triturated with ether (2x100ml) and filtered. The crude residue was chromatographed (silica gel, CH_2Cl_2-MeOH-NH_4OH 90-10-1) to give pure product (1.39 g, 71%) which was recrystallized from EtOAc-CH_3CN, mp 186-88°C. Anal calcd. for $C_{27}H_{34}N_4O_2$: C, 72.60; H, 7.67; N, 12.54. Found C, 72.21; H, 7.91; N, 12.28.

EXAMPLE 61

Preparation of

5-[4-(N-cyclopentyl-N-cyclohexylcarbamoyl)-2-methoxybenzyl]-5H-imidazo[4,5-c]pyridine



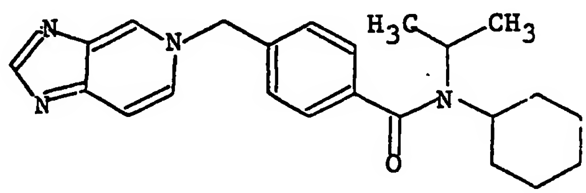
To a stirred solution of 5H-imidazo[4,5-c]pyridine (660mg, 5.57 mmol) in N,N-dimethylacetamide (25ml), 4-bromomethyl-2-methoxy-N-cyclopentyl-N-cyclohexyl benzamide (2.0g, 5.07mmol) was added.

The reaction mixture was stirred under argon at 75°C. After 24h, the reaction flask was cooled to room temperature and the solvent removed under reduced pressure. The residue obtained was diluted with water (650ml) and basified with aq. ammonium hydroxide (20ml). The reaction solution was extracted with chloroform (4x100 ml). The organic layer was washed with brine (3x250 ml), dried ($MgSO_4$) and filtered. The combined filtrate was concentrated and the residue (2.79g) chromatographed (silica gel, CHC_{13}-EtOH-NH_4OH 10-90-1) to give desired product (1.36g, 62%), mp 197-99°C. Anal calcd. for $C_{26}H_{32}N_4O_2$ $0.4H_2O$: C, 71.01; H, 7.52; N, 12.74. Found C, 70.87; H, 7.49; N, 12.70.

EXAMPLE 62

Preparation of

5-[4-(N-isopropyl-N-cyclohexylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine

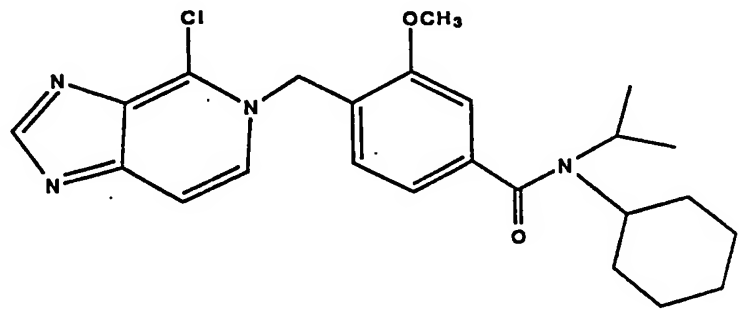


To a stirred solution of 5H-imidazo[4,5-c]pyridine (680g, 5.8mmol) in N,N-dimethylacetamide (30ml), 4-bromomethyl-N-isopropyl-N-cyclohexyl benzamide (2.2g, 6.44mmol) was added. The reaction mixture was stirred under argon at 80-85°C. After 20h, the reaction flask was cooled to room temperature and the solvent removed under reduced pressure at <45°C. The residue obtained was triturated with ether and filtered. The crude residue (1.85g) was chromatographed (silica gel, CH_2Cl_2-EtOH-NH_4OH 80-20-1) to give pure product (1.29 g, 59%) which was recrystallized from EtOAc-CH_3CN, mp 209-10°C. Anal calcd. for $C_{23}H_{28}N_4O$ 0.2H_2O: C, 72.70; H, 7.48; N, 14.75. Found C, 72.92; H, 7.60; N, 14.82.

EXAMPLE 63

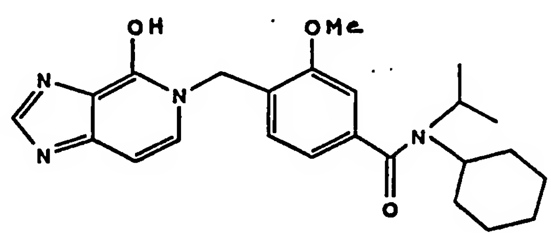
Preparation of

5-[4-(N-cyclohexyl-N-isopropylcarbamoyl)-2-methoxy-benzyl]-4-chloro-5H-imidazo[4,5-c]pyridine

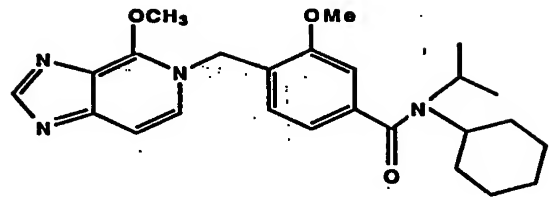


Preparation of the 4-chloro-imidazo[4,5-c]pyridine starting material as well as the 2-methoxy-3-bromo-N-cyclohexyl-N-isopropylbenzamide have been described earlier in this specification. Coupling of the 4-chloro-imidazo[4,5-c] to the 2-methoxy-3-bromo-N-cyclohexyl-N-isopropylbenzamide in dimethylacetamide at 85-90°C for 26h gives the titled compound.

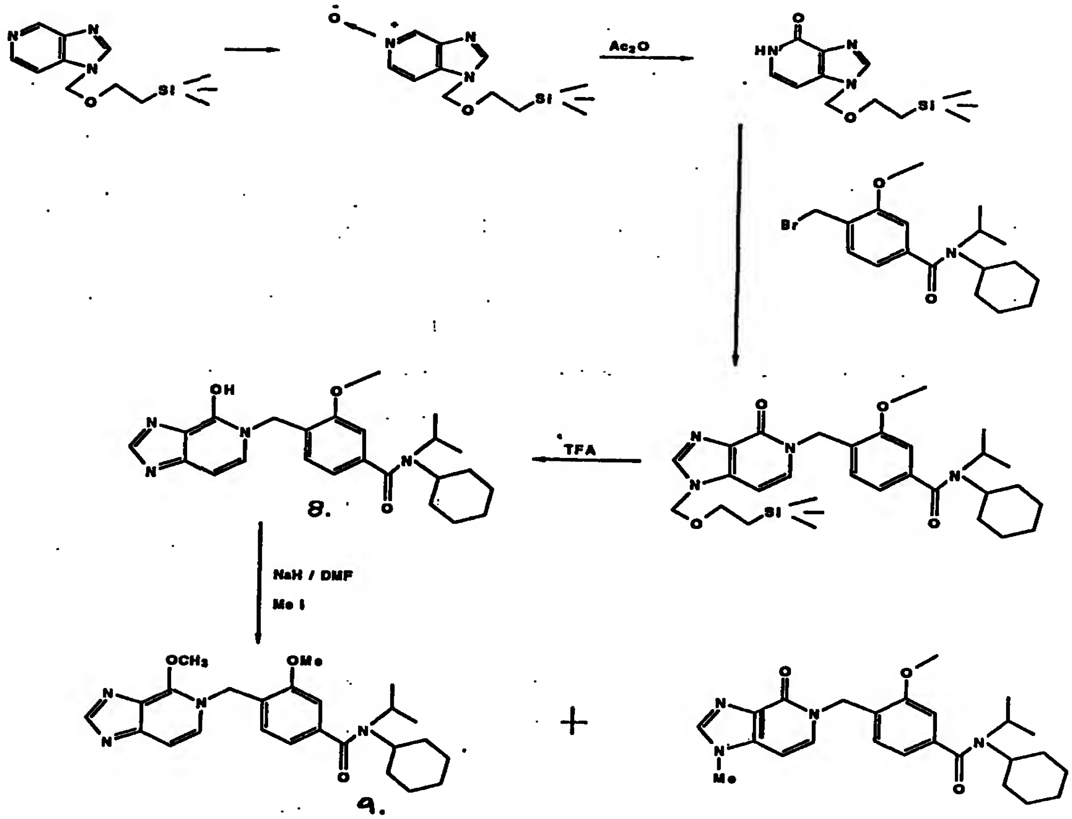
EXAMPLE 64



and



The above compounds can be synthesized according to the following scheme.-



The N-1 compound of 5H-imidazo[4,5-c]pyridine is protected by SEM-Cl and converted to a pyridine N-oxide using m-chloroperbenzoic acid in a manner described for the preparation of 4-chloro-imidazo[4,5-c]pyridine. The pyridine-N-oxide compound is refluxed in acetic anhydride for 4 hrs. to give 4-oxo-1-(2-trimethylsilyl)-ethoxy-methyl-imidazo[4,5-c]pyridine. Reacting this compound with 4-bromomethyl-3-methoxy-N-isopropyl-N-cyclohexyl benzamide in dimethylformamide and sodium hydride at room temperature for 4 hours gives the 5-benzylated product. Cleavage of the SEM-group is accomplished by trifluoro-acetic acid at 50°C for 18 hours to give the compound of formula 8 (titled compound). Treatment of the 4-hydroxy group of the compound of formula 8 with sodium hydride/iodomethane gives the compound of formula 9 (titled compound).

EXAMPLE 65

PAF-induced platelet aggregation and secretion: Washed, [^{3}H]serotonin-labeled rabbit platelets were prepared as previously described in COX, C. P., J. LINDEN and S. I. SAID: VIP elevates platelet cyclic AMP (cAMP) levels and inhibits in vitro platelet activation induced by platelet-activating factor (PAF). Peptides 5:25-28, 1984, and maintained in an atmosphere of 5% CO_2 at 37° C until used in the bioassay. Aliquots of platelets (2.5 x

10^8/ml) were incubated with either an antagonist of PAF or the appropriate vehicle for 60 sec prior to the addition of PAF (0.2 nM to 0.2 μM). Aggregation was continuously monitored on a strip-chart recorder and recorded as the height of the tracing at 60 sec after the the addition of PAF. Secretion of [^{3}H] serotonin was measured in a sample of the platelet suspension removed at 60 sec after the addition of PAF. The percent inhibition of aggregation and secretion was calculated by comparing antagonist-treated platelets with the appropriate vehicle-treated control platelets. Each combination of antagonist and PAF was repeated 12-15 times, using several different platelet preparations. IC_{50} values were determined by inspection of the dose-response curves.

EXAMPLE 66

Inhibition of ^{3}H-PAF Binding to Human Platelet Membrane Receptors

Receptor Preparation: Ten units of in-dated human packed platelets, each containing 45-65 ml platelet rich-plasma, were purchased from a commercial blood bank. Disposable plasticware was used throughout for receptor preparation. The units were pooled and a 1 ml aliquot was removed for determination of platelet concentration, using a Coulter Counter. The remaining platelet rich plasma was dispensed into 50 ml conical tubes and centrifuged at room

temperature for 15 minutes at 3000 RPM (2300 x g). Plasma was decanted and the platelets were resuspended in 35 ml of buffer (10 mM Trizma 7.0, 2 mM EDTA (dipotassium salt), and 150 mM KCl) and transferred to fresh tubes, which were centrifuged again as above. The platelets were washed 3 times, avoiding contaminating erythrocytes at the bottom of the pellets. Pellets were consolidated at each step, and by the last wash with EDTA/KCl buffer, most of the erythrocytes were in 1 tube. The pellets were resuspended in buffer containing 10 mM Trizma 7.0 with 10 mM $CaCl_2$. Following centrifugation, the buffer was decanted and the pellets were resuspended in the $CaCl_2$ buffer, avoiding erythrocyte contamination by recovering less than 100% of the platelet pellets. The resuspended platelets were dispensed in 8-10 ml aliquots into Corex tubes and disrupted by three cycles of freezing (Dry Ice/ethanol) and thawing (24°C). The tubes were centrifuged at 40,000 x g for 20 minutes at 4°C. Supernatants were decanted and each pellet was resuspended in 5-7 ml 10 mM Trizma 7.0. All resuspended pellets were pooled and aliquots of about 1200 µl were dispensed into 1.5 ml microfuge tubes and frozen at -70°C. Protein content was determined by a fluorescamine protein assay.

<u>Assay Methods: Receptor Characterization</u> - Each receptor preparation was evaluated to determine the number of receptor populations, the number of PAF receptor equivalents/mg protein and the dissociation constant

(K_D) for PAF binding. This required 2-3 experiments in which the protein concentration was held constant and the ^{3}H-PAF ligand concentration was varied from approximately 0.10-2.5 nM and the data was analyzed by Scatchard methodology. Total incubation volume was 250 µl for these procedures and incubations were conducted at 24°C for 30 minutes. For further experimentation, total incubation volumes are 500 µl. Protein and ligand concentrations were adjusted to give 0.075 nM receptor equivalents in the presence of 0.75 nM ^{3}H-PAF. Each receptor preparation was then used to determine the dose - response displacement relationship of unlabeled PAF and the PAF antagonist, triazolam. As long as the K_D value and IC_{50} values for PAF and triazolam were consistent with similar data collected from past receptor preparations used in the assay, the new receptor preparation was used for evaluating compounds.

Assay Methods: Routine Assay of Compounds - The compounds were weighed precisely and solubilized in quantities of DMSO such that a 5 µl aliquot in the incubate would deliver the desired compound concentration. Compounds tested for the first time in this assay were evaluated at a concentration of 50 µM in the incubation medium. All compounds were generally solubilized in DMSO for about 2 hours prior to assay. Triazolam was always included in each screening assay as a compound inhibition control. A standard concentration of 50 µM inhibited ^{3}H-PAF

binding by approximately 50%. Nonspecific binding control solution was made by drying to completion about 26.2 µl unlabeled PAF under a stream of argon. PAF was resolubilized in 1000 µl DMSO. When delivered in a 5 µl aliquot, the final concentration of 1 µM PAF in the incubate exceeded by 1000-fold the concentration of ^{3}H-PAF.

All buffers containing proteins were made at room temperature on the day of assay. Assay buffer was prepared by adding 125 mg human albumin to 25 ml of stock buffer (10 mM Trizma 7.4 with 20 mM $CaCl_2$). Rinse buffer was made by adding 20 grams bovine serum albumin to 1000 ml stock buffer. About 80 ml of rinse buffer was decanted into a small pyrex dish and used to soak 65 Whatman GF/C 2.5 cm glass filters. The remaining rinse buffer was poured into a repipet and placed into an ice bath along with the filters.

Ligand for assay was prepared by adding about 10 µl of stock ^{3}H-PAF (DuPont NEN, NET-668) to 14 ml of assay buffer. Since the amount of ^{3}H-PAF in the final incubate was to be 0.75 nM, the actual amount of stock ^{3}H-PAF to be used had to be determined for each lot of material based upon its specific activity.

Membrane receptors for assay were prepared by thawing the appropriate number of tubes at room temperature and adding

membranes to 10 mM Trizma 7.0 containing 10 mM $CaCl_2$. A total volume of 14 ml was made. The actual amount of membranes needed was determined by the requirement to have 0.075 nM PAF receptor equivalents per assay tube. All materials were kept in motion by rocking on a rocker plate.

First, 5 µl of compound or DMSO was added to each 12 X 75 mm polypropylene tube, followed by the addition of 95 µl assay buffer. Next, 200 µl ^{3}H-PAF was added to each tube and 3 aliquots of ^{3}H-PAF taken at different times during the dispensing were placed in scintillation vials. The reaction was initiated by the addition of 200 µl of membranes. All tubes were very briefly vortexed and placed in a 24°C water bath for about 30 minutes. During this time, Whatman GF/C filters were placed on the filter racks of 5 Millipore vacuum manifolds. The incubations were terminated by first adding 4 ml ice-cold rinse buffer to each incubation tube and then decanting them over the filters under vacuum. Tubes and filters were rinsed twice more. Each filter was placed into a 20 ml scintillation vial to which 20 ml Aquasol (DuPont NEN, NDF 952) was added. All vials were given 2 hours in the dark for photo and chemiluminence to dissipate prior to liquid scintillation counting.

In summary, each incubation tube contained 500 µl total volume of incubate. This consisted of 5 µl drug with DMSO or only DMSO, 95 µl assay buffer, 200 µl ^{3}H-PAF

(0.75 nM final concentration) and 200 microleters membrane receptors (0.075 nM final concentration). 60 tubes per assay were run and each dose was performed in triplicate. Controls in every assay consisted of 2 diluent (DMSO) "0" controls (2 triplicate determinations placed at different positions within the 60 tube assay), 1 nonspecific binding control, and 1 triazolam drug control. The 16 remaining doses were used to test 16 different compounds at the screening dose of 50 μM, or to run dose-response determinations for a compound. In general, dose-response curves were composed of 4 compound doses designed to inhibit ^{3}-PAF binding by 15-85%, with at least 1 dose on each side of the 50% point.

Routine Assay Calculations: Triplicate DPM determinations (corrected for background) within a single compound dose were averaged while all 6 determinations of total binding ("0" dose, DMSO only) were averaged. The amount for nonspecific binding (1 μM PAF) was subtracted from all the dose averages, giving an amount of specific binding in all cases. The percent displacement of ^{3}H-PAF or inhibition of binding was calculated by the formula STBo-SBc/STBo x 100, where STBo = specific binding of "0" dose controls and SBc = specific binding in the presence of compound. If a compound tested at the initial screening dose of 50 μM inhibited binding by 45% or more, the compound was considered active and was tested in a dose-response manner to determine an IC_{50} value.

Compounds inhibiting PAF binding by less than 45% at a 50 μM concentration were considered inactive and no further testing was done.

IC_{50} values were determined on active compounds in subsequent tests. Three or more compound doses must inhibit ^{3}H-PAF binding between 15-85%. Using a computer program, % displacement data was transformed (logit) and a least squares linear regression was performed on the data meeting the 15-85% requirement to determine IC_{50} values from data points derived from the same assay.

Compound	PAF induced platelet secretion $(IC_{50})M$	PAF induced platelet aggregation $(IC_{50})M$	Inhibition of ^{3}H-PAF Binding to Human Platelet $(IC_{50})\mu M$
5-[4-(N-methyl-N-cyclohexyl-carbamoyl)benzyl]-5H-imidazo-[4,5-c]pyridine	7.2×10^{-7}	10^{-5} to 10^{-6}	15.2
5-[4-(N-n-octylcarbamoyl)-benzyl]-5H-imidazo-[4,5-c]pyridine	10^{-6} to 10^{-7}	10^{-5} to 10^{-6}	11.0
5-[4-(N-n-decylcarbamoyl)-benzyl]-5H-imidazo-[4,5-c]pyridine	10^{-6} to 10^{-7}	10^{-5} to 10^{-6}	9.71
5-[4-(N-n-dodecylcarbamoyl)-benzyl]-5H-imidazo-[4,5-c]pyridine	1 to 5×10^{-7}	10^{-6} to 10^{-7}	11.9
5-[4-(N-(2-decalyl)-N-methyl-carbamoyl)benzyl]-5H-imidazo-[4,5-c]pyridine	10^{-6}	10^{-5} to 10^{-6}	13.2
5-[4-(N-(4,4-dimethyl-2-pentyl)carbamoyl)benzyl-5H-imidazo[4,5-c]pyridine	10^{-6}	10^{-5}	22.3
5-[4-(N,N-diisopropyl-carbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-7} to 10^{-8}	10^{-5} to 10^{-6}	7.65
5-[4-(N,N-dicyclopentyl-carbamoyl)benzyl]-5H-imidazo-[4,5-c]pyridine	10^{-8} to 10^{-9}	10^{-7} to 5×10^{-8}	0.31
5-[4-(N-cyclohexylcarba-moyl)benzyl]-5H-imidazo-[4,5-c]pyridine	10^{-6} to 10^{-7}	10^{-5}	19.3
5-[4-(N-ethyl-N-cyclohexyl-carboxamido)carbamoyl)-benzyl]-5H-imidazo-[4,5-c]pyridine	10^{-7} to 10^{-6}	10^{-6} to 10^{-5}	5.20
5-[4-(N-isopropyl-N-cyclohexyl carbamoyl)benzyl]-5H-imidazo-[4,5-c]pyridine	10^{-8}	10^{-7} to 10^{-8}	0.17
5-[4-(N-sec.butyl-N-cyclo-hexylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-8} to 10^{-9}	10^{-7} to 5×10^{-8}	0.58
5-[4-(N-isobutyl-N-cyclo-hexylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-7}	10^{-6}	2.82

Compound	PAF induced platelet secretion (IC_{50})M	PAF induced platelet aggregation (IC_{50})M	Inhibition of ^{3}H-PAF Binding to Human Platelet (IC_{50})μM
5-[4-(N-(3-pentyl)-N-cyclohexylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-7} to 10^{-8}	10^{-6} to 10^{-7}	--
5-[4-(N-cyclopropyl-N-cyclohexylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-6} to 10^{-7}		3.68
5-[4-(N-cyclobutyl-N-cyclohexylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-8} to 10^{-9}	10^{-7} to 10^{-8}	0.0199
5-[4-(N-cyclpentyl-N-cyclohexylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-8} to 10^{-9}	10^{-7} to 10^{-8}	0.32
5-(4-(N,N-dicyclohexylcarbamoylbenzyl)-5H-imidazo[4,5-c]pyridine	10^{-8}	10^{-6} to 10^{-7}	1.06
5-[2-[4-(N-methyl-N-cyclohexylcarbamoyl)phenyl]ethyl]-5H-imidazo[4,5-c]pyridine	10^{-5} to 10^{-6}	10^{-4} to 10^{-5}	--
5-[3-[4-(N-methyl-N-cyclohexylcarbamoyl)phenyl]propyl]-5H-imidazo[4,5-c]pyridine	10^{-5} to 10^{-6}	10^{-4} to 10^{-5}	61.1
5-[4-(N,N-dicyclopentylcarbamoyl)-2-methoxybenzyl]-5H-imidazo[4,5-c]pyridine	10^{-8} to 10^{-9}	10^{-7} to 10^{-8}	0.055
5-[4-(N-cyclohexyl-N-cyclopentylcarbamoyl)-2-methoxybenzyl]-5H-imidazo[4,5-c]pyridine	10^{-8} to 10^{-9}	10^{-8}	0.0302
5-[4-(N-isopropyl-N-cyclohexylcarbamoyl)-2-methoxybenzyl]-5H-imidazo[4,5-c]pyridine	10^{-8}	10^{-7} to 10^{-8}	0.0665

Compound	PAF induced platelet secretion $(IC_{50})M$	PAF induced platelet aggregation $(IC_{50})M$	Inhibition of ^3H-PAF Binding to Human Platelet $(IC_{50})\mu M$
5-[4-(N-methyl-N-cyclohexylcarbamoyl)-2-methoxybenzyl]-5H-imidazo[4,5-c]pyridine	10^{-6} to 10^{-7}	10^{-5} to 10^{-6}	--
5-[4-(N-cyclopentyl-N-cyclohexylcarbamoyl)-2-fluorobenzyl]-5H-imidazo-[4,5-c]pyridine	10^{-8} to 10^{-9}	10^{-7} to 10^{-8}	0.0755
5-[4-(N-isopropyl-N-cyclohexylcarbamoyl)-2-fluorobenzyl]-5H-imidazo[4,5-c]pyridine	10^{-7} to 10^{-8}	10^{-7} to 10^{-8}	0.442
5-[4-(N-methyl-N-cyclohexylcarbamoyl)-2-fluorobenzyl]-5H-imidazo[4,5-c]pyridine	10^{-6} to 10^{-7}	10^{-5} to 10^{-6}	--
5-[4-(N-tert.butyl-N-cyclohexylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-8} to 10^{-9}	10^{-7} to 10^{-8}	87.7% inhib (50μM)
5-[4-(N-phenyl-N-cyclopentylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-6} to 10^{-7}	10^{-6}	2.35
5-[4-(N-(3-methylcyclohexyl)-N-cyclopentylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-8} to 10^{-9}	10^{-7} to 10^{-8}	0.074
5-[4-(N-(4-methylcyclohexyl)-N-cyclopentylcarbamoyl)benzyl]-5H-imidazo[4,5-c]pyridine	10^{-7} to 10^{-8}	10^{-6} to 10^{-7}	0.75
5-[3-(N-methyl-N-cyclohexylcarbamoyl)benzyl]-5H-imidazo-[4,5-c]pyridine	10^{-4} to 10^{-5}	10^{-4} to 10^{-5}	38% inhib (50μM)
5-[3-(N-isopropyl-N-cyclohexylcarbamoyl)benzyl]-5H-imidazo-[4,5-c]pyridine	10^{-5} to 10^{-6}	10^{-4} to 5×10^{-5}	26.1% inhib (50μM)
5-[4-(N,N-dicyclopentylcarbamoyl)benzyl]-4-methyl-5H-imidazo[4,5-c]pyridine	10^{-7} to 10^{-8}	10^{-7} to 10^{-8}	0.188
5-[4-(N,N-dicyclopentylcarbamoyl)benzyl]-2-methyl-5H-imidazo[4,5-c]pyridine	10^{-6} to 10^{-7}	10^{-5} to 10^{-6}	70.8% inhib (50μM)

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KÖZZÉTÉTELI PÉLDÁNY

Eljárás szubsztituált nitrogén tartalmú heterociklusos vegyületek szintézisére

Bejelentő, feltaláló

Horváth András	Tiszadob, ~~Károlyi Mihály út 17/b.~~	80 %
Salamon Zoltán	Debrecen, ~~Egressy Béni tér 8.~~	20 %

A bejelentés napja: 1995. 03. 31.

Debrecen, 1995. január

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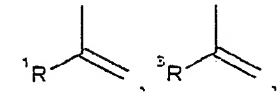
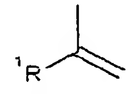
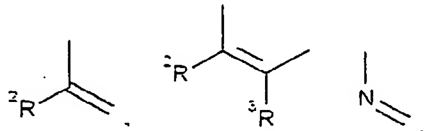
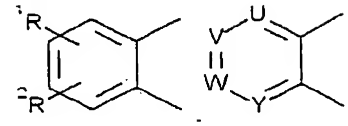
Találmányunk tárgya új, általánosan alkalmazható eljárás, szubsztituált, esetenként homo- vagy heterociklussal kondenzált, N-szubsztituált, legalább két N-atomot tartalmazó azolok előállítására.

A találmányunk szerint előállított azolok biológiailag aktív anyagok intermediereként hasznosithatók és/vagy fungicid, baktericid, antitrombotikus, gyulladáscsökkentő, antivirális ill. herbicid hatású vegyületek (Vanden Bossche, H.; Lauwers, W.; Willemsens, G.; Marichal, P.; Cornelisson, F.; Cools, W. *Pestic. Sci.* 1984, *15*, 188; Fiddler, G. I.; Lumley, P. *Circulation* 1990, *81* (Suppl. I), I 69; Wright, S. W.; Harris, R. R.; Collins, R. J.; Corbett, R. L.; Green, A. M.; Wadman, E. A.; Batt, D. G. *J. Med. Chem.* 1992, *35*, 3148; Umarov, A. A.; Khalikov, S.S.; Khaidarov, M.; Tyurina, L. A. *Uzb. Khim. Zh.* 1989, *1*, 40; *Chem. Abstr.* 1989, *111*, 110920; McKellar, Q. A.; Scott, E. V. *J. Vet. Pharmacol. Ther.* 1990, *13*, 223; Shirakura, S.; Karasawa, A.; Kubo, K. *Arzneim.-Forsch.* 1991, *42*, 1242; Nicolai, E.; Goyard, J.; Benchetrit, T.; Teulon, J. M.; Caussade, F.; Virone, A.; Delchambre, C.; Cloarec, A. *J. Med. Chem.* 1993, *36*, 1175; Montgomery, J. A.; Clayton, S. J.; Thomas, H. J.; Shannon, W. M.; Arnett, G.; Borner, A. J.; Kion, T. K.; Cantoni, G. L.; Chiang, P. K. *J. Med. Chem.* 1982, *25*, 626; Spratt, T. E.; de los Santos, H. *Biochemistry* 1992, *31*, 3688; Ger. Offen. 1 966 806, U.S. Appl. 754 490, C.A. 1975, 82, 150 485).

Fiziológiailag aktív alkaloidok kulcs intermedierei, pl. pilokarpin és analógjai szintézisében az 1-metil-imidazol-5-karboxilátok (Kirchlechner, R.; Casutt, M.; Heywang, U.; Schwarz, M.W. Synthesis 1994 247;Dener, J.M.; Zhang, L.-H.; Rapoport, H. J. Org. Chem. 1993, 58, 1169). Ismeretes (Testa, B.; Jenner, P. *Drug Metab. Rev.* 1981, *12(1)*, 1-117 (30. o.); Wahhab, A.; Smith, J. R.; Ganter, R. C.; Moore, D. M.; Hondrelis, J.; Matsoukas, J.; Moore, G. J. *Arzneim.-Forsch.* 1993, *43*, 1157 (1163 o.)), hogy a citokróm P-450 enzimekhez való kötődés, így a biológiai hatás a sztérikusan kevésbbé gátolt nitrogén atomot tartalmazó azolok (pl. 1,5-szubsztituált imidazolok szemben az 1,4-szubsztituáltakkal) esetében lényegesen erősebb a kevésbé stabil regioizomereknél. Cosar és munkatársai összevetették az 5- illetve 4-nitro-1-alkil-imidazolok trichomonas elleni illetve baktericid hatását és az 5-izomer/ minden esetben erősebbnek mutatkozott (Cosar, C.; Crisan, C.; Horclois, R.; Jacob, R. M.; Robert, J.; Tchelitcheff, S.; Vaupre, R. *Arzneimittel-Forsch.* 1966, *16(1)*, 23). Találmányunk tárgya szerint eljárva, egyebek mellett előnyösen állithatók elő ezek a kevésbé stabil izomerek.

Találmányunk tárgya eljárás az 1. általános képletű azolok előállítására,

ahol A jelentése —,  B jelentése 

D jelentése  BD jelentése 

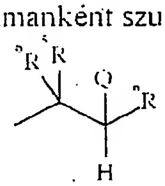
illetve R^1, R^2, R^3 jelentése H, alkalmanként szubsztituált C_{1-4}alkil, (szubsztituált)fenil, $NHCOC_{1-4}$alkil, $COOC_{1-4}$alkil

U, V, W, Y, Z jelentése CH, N, CO, CS, N-C_{1-8}alkil, C-OC_{1-4}alkil, C-SC_{1-4}alkil, C-N(C_{1-4}alkil$)_2$

n jelentése 0, 1

X jelentése klór-vagy bróm-vagy jód atom, C_{1-4}alkilSO_3, OSO_2R^7, C_{1-4}fluórozottalkil-SO_3, (szubsztituált)fenil-SO_3,

illetve R^7 jelentése -, H, alkalmanként szubsztituált C_{1-8}alkil, N-tartalmú heteroaril

R^8 jelentése -, H, 

R^4, R^5, R^6 jelentése H, alkil, cikloalkil, Q

illetve Q jelentése ~~CN, $COOC_{1-4}$alkil, COC_{1-4}alkil~~, CO(szubsztituált)fenil, SO_2C_{1-4}alkil, SO_2(szubsztituált)fenil

oly módon, hogy

a.) az NH csoportot tartalmazó 2. általános képlettel jellemzett azolok,

ahol A, B, D jelentése a fenti,

a 3. általános képlettel jellemzett α, β-telítetlen vegyületekkel,

ahol R^4, R^5, R^6 jelentése a fenti

a bázisként és/vagy transzfer reagensként funkcionáló 4. általános képletű amidinnel,

ahol E, J, L jelentése -, H, alifás gyűrű maradék, N-tartalmú alifás gyűrű maradék

az 1. képlet alesetét képező 5. általános képletű N-(szubsztituált)etilén származékot adják,

ahol A, B, D, R^4, R^5, R^6, Q jelentése a fenti,

b.) az 5. általános képletű azolok a 6. általános képlettel jellemezhető alkilezőszerrel,

ahol X jelentése a fenti

kvaterner sóvá alakítása, majd az a.) pont szerint felvitt (szubsztituált)etilén csoportot bázissal szelektíven egy Hofmann-típusú lebontásban való eltávolításával a kevésbé preferált 1. általános képletű alkil-azolokat kapjuk.

Eljárásunk a.) pontja szerint eljárva, a 2. általános képletű öttagú N-tartalmú heterociklusos vegyületet vagy gyűrűkondenzált származékát 0-150°C-on a 4. általános képletű szerves amidin jellegű bázis katalizátor, (szubsztituált)-guanidin bázis, célszerűen 1,5,7-triazabiciklo[4.4.0]dec-5-én (TBD) vagy ennek 7-metil származéka (7-Me-TBD) vagy ennek

polimer hordozóra felvitt változata (TBD-P) jelenlétében, poláros-aprotikus oldószerben, pl. acetonitrilben, nitrometánban, acetonban, dimetilszulfoxidban, N,N-dimetil-formamidban, N,N-dimetil-acetamidban, N-metil-2-pirrolidonban, vagy ezek keverékében, előnyösen acetonitrilben reagáltatjuk 1-10 mólekvivalens 3. általános képletű α,β-telítetlen vegyülettel.

— a reakcióelegyet — hordozóra felvitt katalizátor alkalmazása esetén megszűrve — bepároljuk,

— vagy vízzel ill. szervetlen só, előnyösen ammónium-klorid vagy ammónium-karbonát vizes oldatával kezelve, szűrve izoláljuk az 1. képlet alesetét képező 5. képletű terméket.

Eljárásunk **b.)** pontja szerint eljárva,

— az a.) pont szerint előállított 5. általános képlettel jellemzett terméket tartalmazó reakcióelegyhez,

— vagy az a.) pont szerint előállított 5. általános képletű terméket poláros oldószerben, így nitrometánban, alkoholokban, dimetilszulfoxidban, N,N-dimetil-formamidban, N,N-dimetil-acetamidban, N-metil-2-pirrolidonban, előnyösen acetonitrilben felvéve,

0,001-1 mólekvivalens halogenid-ionos katalizátort, előnyösen alkáli-jodidot beadva kapott oldathoz, a bevitt azolra számítva 0,9-10 mólekvivalens 6. általános képletű alkilezőszerrel 0-150°C-on reagáltatjuk,

— a kapott reakcióelegyet bepároljuk, a nyert nyers azólium sót feloldjuk vízben és vízzel nem elegyedő oldószerrel a vizes fázist mosva az 1. általános képlet alesetét jelentő 7. általános képletű vegyület vizes oldatát kapjuk.

— vagy a nyert reakcióelegyhez vagy annak párlási maradékához aprotikus oldószert, így étert, acetont, etilacetátot adva, az elegyből lehűlve kivált 1. általános képlet alesetét jelentő 7. általános képletű terméket szűrve izoláljuk,

majd a valamely fenti módszerrel kapott, az 1. általános képlet alesetét képező

— 7. általános képletű azólium sóhoz

— vagy az azt tartalmazó reakcióelegyhez

— vagy vizes oldatához

0,95-5 ekvivalens bázist, előnyösen alkáli-alkoholátot, alkáli-hidroxidot, alkáli-karbonátot, alkáli-hidrogénkarbonátot, amin származékot vagy ezek alkoholos és/vagy vizes oldatát adjuk, 0-100°C-on kevertetjük,

— lehűtjük, vízzel és/vagy ammóniumsó, előnyösen ammónium-klorid vagy ammónium-karbonát 10-30 %-os oldatával kezelve, a kivált 1. általános képletű (n=0, R^x= —) terméket szűréssel izoláljuk,

— vagy a kapott reakcióelegyet valamely adszorbenssel, előnyösen szilikagéllel, alumíniumoxiddal, derítőszénnel vagy ezek keverékével kevertetjük, szűrjük, az 1. általános képletű (n=0, R^x= —) terméket a szűrlet bepárlásával nyerjük,

— vagy a nyert reakcióelegyből, amennyiben szerves oldószert tartalmaz, vákuumban eltávolítjuk az oldószert, a maradékot vízben felvesszük, vízzel nem elegyedő oldószerrel extraháljuk, a szerves fázist derítjük, szárítjuk, bepároljuk.

Az irodalom szerint a 2. általános képletű azolok közvetlen alkilezése alkilezőszerekkel általában olyan keverékekhez vezet, amelyben a különböző regioizomerek (ahol ez lehetséges) és az N,N'-dialkil kvaterner azolium sók egyaránt jelen vannak. Bár az elválasztás némely ritka esetekben megvalósítható, az olyan esetekben, ahol regioizomerek képződhetnek, a közvetlen alkilezéskor a preferáltabb regioizomer mindig túlsúlyban keletkezik.

A kevésbé preferált izomerek szabad NH csoportot tartalmazó azolokból való előállítására ismeretesek olyan eljárások, amelyben a közvetlen alkilezésben preferált N-atomot védőcsoporttal védik, majd az így védett azolt kvaternerezik, végül a védőcsoportot hasítják. Így hisztidint és származékait benzilezik, majd alkilezés után a benzil védőcsoportot palládium katalizátor felett hidrogenolizálják (Sauerberg, P.; Chen, J.; WoldeMussie, E.; Rapoport, H. *J. Med. Chem.* **1989**, *32*, 1322). Trialkil-9-metil-xantin származékok szintézi-séhez 7-benzil-ill. 7-metoximetil-xantinokat alkalmaztak (von Schuh, H. G. Ger. Pat. 1 113 696, C.A. **1962**, 56, 12 909). Nitroimidazolok esetén alkalmazták a vizes közegben forralva eltávolítható acetoxi-metilén védőcsoportot (Bonnamas, C.; Massonneau, V.; Mulhauser, M.; Rouy, N. *Eur. Pat. Appl.* EP 325,512 (26. Jul. 1989); *Chem. Abstr.* **1990**, *112*, 77185), (4-szubsztituált)-imidazolok, 1,2,4-triazol, benztriazol esetén a hidrolízissel szintén eltávolítható acil-csoportot (Olofson, R. A.; Kendall, R. V. *J. Org. Chem.* **1970**, *35*, 2246. Kashima,C.; Harada,Y.; Hosomi,A. *Heterocycles* **1993**, *35*, 433. Kamijo,T.; Yamamoto,R.; Harada,H.; Iizuka,K. *Chem Pharm. Bull.* **1983**, *31(4)*, 1213), urokaninsav (imidazol-4-akril-sav) észtereknél az ecetsav-cink rendszerrel eltávolítható fenacilt (Lauth-de Viguerie, N.; Sergueeva,N.; Damiot,M.; Mawlawi,H.; Riviere,M.; Lattes, A. *Heterocycles* **1994**, *37*, 1561).

Az alkil típusú (benzil, fenacil, aciloxi-metilén) védőcsoportok közös hátránya, hogy felvitelük nem kellően regioszelektív; a védett azol csak alacsony hozammal és tisztaságban nyerhető. Az acil (acetil, etoxikarbonil, benzoil) védőcsoportok alkalmazása előnyösebb ilyen szempontból, felvitele teljesen regioszelektívnek mondott, azonban az így kapott védett azolok, az acil csoport erős elektronszívó tulajdonsága miatt, csak igen aktív és nehezen előállítható alkilezőszerekkel (trialkiloxónium tetrafluoroborátokkal) vagy magas hőmérsékleten és nyomáson (7000 barig) kvaternerezhetők. Ismert továbbá, hogy az acilezett azolok nehezen tárolható, nedvesség hatására gyorsan bomló vegyületek.

Irodalmi előzmények, illetve tapasztalataink szerint regioszelektivitása miatt a 2. általános képletű azolok esetében speciális alkilezőszer a cianetil csoport.

Imidazolokat termikusan reagáltattak (szubsztituált)akrilnitrillel (Sawa, N.; Okamura, S. *Nippon Kagaku Zasshi* **1969**, *90(7)*, 704; *Chem. Abstr.* **1969**, *71*, 101773. Yamauchi, M.; Masui, M. *Chem. Pharm. Bull.* **1976**, *24(7)*, 1480 Wright, W. B.; Press, J. B. *US 4,619,941* (28. Oct. 1986); *Chem. Abstr.* **1987**, *106*, 102285).

Bázikus katalízissel cianetileztek 4-arilimidazolt etanolban kálium-hidroxid jelenlétében (Iradyan, M. A.; Torosyan, A. G.; Mirzoyan, R. G.; Badalyants, I. P.; Isaakyan, Z. S.; Manucharyan, D. Sh.; Dayan, M. Kh.; Sakanyan, G. S.; Dzagatspanyan, I. A.; Akonyan, N.

E.; Ter-Zaharyan, Y. Zh.; Aroyan, A. A. *Khim.-Pharm. Zh.* 1977, *11*, 42; *Chem. Abstr.* **1978**, *88*, 22759y, illetve kvaterner ammónium-hidroxid katalizátorokkal, különböző - főként dioxán - oldószerben, így benzil-trietil/trimetil-ammónium-hidroxiddal 4-nitroimidazolt (Cosar, C.; Crisan, C.; Horclois, R.; Jacob, R. M.; Robert, J.; Tchelitcheff, S.; Vaupre, R. *Arzneimittel-Forsch.* **1966**, *16(1)*, 23) benzimidazolt (Diamond, J.; Wohl, R. A. *Eur. Pat. Appl.* 34,116 (19 Aug 1981); *Chem. Abstr.* **1981**, *95*, 203961), 5-nitro-, 2-metil-5-nitro-benzi-midazolt (Efros,A.M. *Zhur. Obsh. Khim.* **1960**, *30*, 3565; *Chem. Abstr.* **1961**, *55*, 18712d).

Imidazolt reagáltattak fenil-vinil-ketonnal tetrabutil-ammónium hidroxid katalízissel (Bogatkov, S. V.; Kormanskaya, B. M.; Mochalin, V.; Cherkasova, E. M. *Khim. Geterotsikl. Soedin.* **1971**, *7(5)*, 662-4; *Chem. Abstr.* 1972, *76*, 59525).

Vizsgálták különböző körülmények között 1,2,3-triazol illetve benztriazol Michael-addícióit benzil-trimetil-ammónium hidroxid, illetve piridin katalízissel (Wiley, R. H.; Smith, N. R.; Johnson, D. M.; Moffat, J. *J. Am. Chem. Soc.* 1954, *76*, 4933). 2-metil-4-nitroimidazol reakcióját 5-féle Michael-akceptorral, számos katalizátorral különféle oldószerekben, s legjobbnak a piridin-dimetilszulfoxid rendszert találták. Ilyen körülmények között az akrilnitril 135°C-on, 10 óra alatt elreagál (Rao,A.K.S.B.; Rao,C.G.; Singh,B.B. *J. Org. Chem.* 1990, *55*, 3702). Egyéb tercier amin katalizist írnak le imidazol és metilakrilát reakciójában trietil-amin jelenlétében (Bogatkov, S. V.; Kormanskaya, B. M.; Mochalin, V.; Cherkasova, E. M. *Khim. Geterotsikl. Soedin.* 1971, *7(5)*, 662-4; *Chem. Abstr.* 1972, *76*, 59525). Természetes eredetű xantin származékokat, így teofillint akrilnitrillel réz-szulfát jelenlétében nátrium-metilát, illetve benzil-trimetil-ammónium-hyroxid katalízissel (Doebel, K.; Spiegelberg, H. *US 2,761,862* (1956); *Chem. Abstr.* **1957**, *51*, 3676. Rybar, A.; Stibrányi, L. *Collect. Czech. Chem. Commun.* **1973**, *38(5)*, 1571). teofillint, teobromint reagáltattak akrilnitril, akrilsav, etilakrilát, fenil-vinil keton reagensekkel benziltrimetil-ammónium-hidroxid jelenlétében (Zelnik, R.; Pesson, M. *Bull. Chem. Soc. Fr.* 1959, 1667).

Ezek az eljárások általában magas hőmérsékletet, hosszú reakcióidőket követelnek meg, ami a regioszelektivitás romlásához, mellékreakciókhoz vezet (pl. a Michael-akceptor polimerizációja, a rendszerben levő nem azol típusú komponensek addíciója a Michael-akceptorra). A mellékreakciók és az alkalmazott magas forráspontú oldószerek nehezítik a termék kinyerését a reakcióelegyből, csökkentik a hozamot, rontják a termék minőségét.

Alkalmaztak cianetil védőcsoportot imidazol és benzimidazol alkilezéséhez is (Horváth, A. *Synthesis*, 1994, 104), de a megadott eljárás körülményes, nagy anyagveszte-séggel járó feldolgozási procedúrát igényel (savas átoldás-extrakció-visszalúgozás-újabb extrakció), ugyanakkor nem vizsgálták a regioszelektivitást. Az alkalmazott bázisok (nátrium-hidroxid, nátrium-alkoholát) nem alkalmazhatók egyrészt erős elektronszívó csoportokkal szubsztituált azolok (például nitroimidazolok) esetében, ahol az N-alkil-N'-cianetil-azolium kvaterner sóból nem a cianetil, hanem az alkil csoport lehasadása preferált, másrészt nukleofil bázisra érzékeny molekulák esetén (a ftalimido gyűrű például ezen bázisok hatására felnyílik).

Találmányunk szerinti eljárás előnye, hogy egyrészt a szabad NH csoportot tartalmazó 2. képletü azolokat és gyürükondenzált származékaikat az erös, nem nukleofil, a Michael addiciót kiváltó bázis és/vagy transzfer reagensként funkcionáló 4. általános képletü amidin vagy guanidin bázis jelenlétében reagáltatjuk, ami lehetövé teszi, hogy a reakciók gyorsan, enyhe körülmények között, alacsony hömérsékleten (többnyire szobahöfokon) magas hozamban, gyakorlatilag mellékreakciók nélkül, regioszelektíven a kinetikailag előnyben részesitett, stabilabb, az 1. általános képlet alesetét képező 5. általános képletü — a 3. általános képletü vegyület, a Michael akceptor, Q-elektronszivó funkciós csoportjának átalakitásával intermedierként önmagukban is jól hasznosítható — N-(szubsztituált)etilén származékot adják, amely Michael-adduktok magas hozamban és tisztaságban, egyszerü módszerekkel preparálhatók. A gyakorlatilag szelektív teljes konverzió számos esetben lehetövé teszi, hogy további alkilezés esetén a Michael-adduktokat ne izoláljuk a reakcióelegyböl.
A találmányunk szerinti eljárás másrészt a Michael-adduktokat, mint a preferált hely-zetben N-védett azolokat, a kevésbé preferált N-szubsztituált regioizomerek elöállitására hasz-nositja: alkilezöszerekkel kvaternerezve a kapott 7. általános képletü N,N'-diszubsztituált azo-lium sók—alkalmanként izolálva; rendszerint kristályosan izolálható vegyületek, amelyek vár-hatóan szintén rendelkeznek egyéb előnyös tulajdonságokkal—in situ Hofmann-típusú lebon-tás körülményei között a (szubsztituált)etil védőcsoportot szelektiven lehasitva kapott termék a kiindulási azol (kevésbbé preferált) N-szubsztituált származéka. Mind a kvaternerezés, mind a kvaterner só bontása enyhe körülmények között, gyakorlatilag kvantitativan megvalósitható, így a végtermékeket regioszelektiven, magas hozamban, nagy tisztaságban nyerjük.
A ciánetil vagy szubsztituált származéka, mint védőcsoport alkalmazása különösen előnyös azokban az alkilezési esetekben, amikor az 1. általános képletü termékek vizben kevéssé oldódnak és a kvaterner sók a deciánetilezési reakcióelegyböl szüréssel kinyerhetök. A 2-(alkoxikarbonil)etil védőcsoportok alkalmazása vizben oldódó 1. általános képletü végtermé-kek esetén előnyös, mert a védőcsoport hasitásakor egy vizben jól, szerves oldószerekben rosszul oldódó β-szubsztituált-propionsav só keletkezik, ami a szerves oldószerbe extrahált terméket nem szennyezi.
Erös elektronszivó hatású csoportokkal C-szubsztituált, szabad NH csoportot tartal-mazó azolok kevésbbé preferált N-szubsztituált regioizomerjeinek szintézisére előnyösen a 2-helyzetben keto- vagy szulfonil-csoporttal szubsztituált-etil védőcsoportokat alkalmazunk, ami lehetövé teszi eltávolitásukat viszonylag gyenge, nem nukleofil bázisokkal, így a nukleofilekre érzékeny (gyürüfelnyilás, aromás nukleofil szubsztitúció) erös elektronszivó csoporto(ka)t tartalmazó kvaterner azólium sók mellékreakciók nélküli bontása is megvalósitható.
Eljárásunk részleteit az alábbi példákon mutatjuk be, anélkül, hogy találmányunkat azokra korlátoznánk.

Példák

1.) 4-Fenil-1*H*-imidazol-1-propánsavnitril

4,32 g 4-fenilimidazolt, 3,6 ml akrilnitrilt, 0,14 g TBD-t 10'-et kevertetve 10 ml acetonitrilben, bepárolva kapott maradékhoz ammónium-klorid oldatot adunk, hütjük, kevertetjük, szűrjük, mossuk, szárítjuk. Kitermelés: 5,65 g (95%). o.p. 114-115,5°C.

2.) 4-Nitro-1*H*-imidazol-1-propánsavnitril

5,65 g 4-nitroimidazolt, 5 ml akrilnitrilt és 0,28 g TBD-t 15 ml DMSO-ban kevertetünk 100 °C-on 5 órát. Bepárolva az 1.) példával azonos módon dolgozzuk fel. Kitermelés: 7,8 g (94 %). etil-acetátból átkristályositva o.p. 112-113 °C.

3.) α,4-Dimetil-1*H*-benzimidazol-1-propánsavnitril

2,64 g 4-metil-benzimidazolt. 1,67 g krotonsavnitrilt és 0,14 g TBD-t 50°C-on kevertetünk 10 ml acetonitrilben 1 órát. Bepároljuk, az előző példával azonos módon dolgozzuk fel. Kitermelés: 3,82 g (96 %), o.p. 117-118 °C. ^{1}H NMR($CDCl_3$): 1,89 (d, 3H, J= 7,1), 2,69 (s, 3H), 2,88-2,98 (m, 2H), 4,83 (sext. 1H, J= 7,1), 7,10-7,17 (m, 1H), 7,18-7,31 (m, 2H), 8,03 (s, 1H). MS(EI$^+$, 70 eV): m/z (%): 199 (M$^+$, 28), 159 (100), 131 (15), 77 (16).

4.) 1*H*-1,2,4-Triazol-1-propánsavnitril

34,52 1,2,4-triazolt, 50 ml akrilnitrilt és 0,7 g TBD-t felveszünk 50 ml acetonitrilben, 4 órát kevertetjük, bepároljuk. Kitermelés 65,16 g. O.p. 36-37 °C (hexán-EtOAc). NMR ($CDCl_3$): 3,00 (t, 2H), 4,47 (t, 2H), 8,01 (s, 1H), 8,23 (s, 1H):

5.) 1*H*-1,2,4-Triazol-1-propánsav etilészter

6,9 g 1,2,4-triazolt, 12 g akrilsav etilésztert és 0,28 g TBD-t felveszünk 20 ml acetonitrilben, 5 órán át kevertetjük, majd bepároljuk. A nyers terméket kromatográfiásan tisztítjuk kloroform : metanol 100:5 elegyel eluálva, 15,8 g (93 %) olajat nyerünk. ^{1}H NMR($CDCl_3$): 1,23 (t, 3H), 2,91 (t, 2H), 4,14 (q, 2H), 4,48 (t, 2H), 7,93 (s, 1H), 8,16 (s, 1H).

6.) 3-(4-metil-1*H*-imidazol-1-il)pentándikarbonsav dietilészter

8,2 g 4-metilimidazolt, 18,6 g dietilglutakonátot és 0,7 g TBD-t 20 ml acetonitrilben 40 napon át állni hagyunk, majd bepároljuk. A nyers-terméket híg sósav oldatból derítjük, kémhatását ammóniaoldattal pH 8-ra állítjuk, diklórmetánnal extraháljuk, a szerves fázist szárítjuk, bepároljuk. Kitermelés: 18,2 g (68 %).

7.) 1-(Fenilmetil)-5-metil-1*H*-imidazol

2,68 g 6.) példa szerint kapott terméket, 1,88 g benzilbromidot 5 ml acetonitrilben visszacsepegő hűtő alatt forraljunk 3 órát, bepároljuk. 10 ml 2 M-os etanolos NaOEt oldatot adunk be, 10' kevertetés után bepároljuk, hidegen híg sósavval savanyítjuk, éterrel mossuk. A vizes fázist szobahőfokon derítjük, ammónia oldattal pH 8-ra állítjuk, hűtjük, szűrjük, vízzel

mossuk, kitermelés 1,04. O.p. 107-109,5 °C (hexán-éter). ^{1}H NMR($CDCl_3$): 2,08 (s, 3H), 5,04 (s, 2H), 6,82 (m, 1H), 6.98-7.10 (m. 2H), 7,22-7,40 (m, 3H). 7.46 (m, 1H).

8.) 1-(2-Cianoetil)-4-fenil-3-metil-1*H*-imidazolium bromid

4,61 g 4-fenilimidazolt. 2,6 ml akrilnitrilt és 1 g TBD-P-t szobahőfokon kevertetünk 20 ml acetonitrilben 130 órát, szűrjük, a szűrlethez 4,3 ml metiljodidot adunk, 6 órát visszacsepegő hűtő alatt forraljuk, lehűtjük, szűrjük, acetonnal mossuk és szárítjuk. Kitermelés: 9,0 g (83 %), o.p. 179,5-180,5 °C (acetonitril). ^{1}H NMR(DMSO-d_6): 3,27 (t, 2H), 3,88 (s, 3H). 4,56 (t, 2H), 7,60 (s. 5H), 8.06 (m. 1H), 9,34 (m, 1H).

9.) 1-(2-Cianoetil)-3-(3-cianopropil)-4-fenil-1*H*-imidazolium bromid

1,97 g 1.) példa szerint előállított terméket. 1.48 g 4-brómbutironitrilt és 0,015 g NaI-ot 5 ml nitrometánban visszacsepegő hűtő alatt forralunk. lehűtjük, 20 ml éterrel hígítjuk, szűrjük, éterrel mossuk és szárítjuk. Kitermelés: 3.21 g (93 %). o.p. 131-132 °C (MeCN). ^{1}H NMR(DMSO-d_6): 1,99 (quint, 2H, *J*= 7,2), 2,58 (t. 2H, *J*= 6,7), 3,33 (t. 2H. *J*= 6,2). 4,33 (t, 2H, *J*= 7,2), 4,60 (t, 2H, *J*= 6,2). 7.60 (s. 5H), 8.11 (d. 1H. *J*= 1,5), 9,60 (d, 1H, *J*= 1,5).

10.) 1-(2-Ciano-1-metil-etil)-3-(3-cianopropil)-4-metil-1*H*-benzimidazolium bromid

A 3.) példa termékéből 1,99 g, 1,48 g 4-brómbutironitrilből a 9.) példa szerint eljárva, kitermelés 3,26 g (94 %), o.p. 187-188 °C (nitrometán). ^{1}H- NMR (DMSO-d_6): 1,78 (d, 3H, *J*= 6,6). 2,30 (quint, 2H, *J*= 6,5). 2,77 (t. 2H. *J*= 6,5), 2,81 (s. 3H). 3,40 (d. 2H, *J*= 6,0), 4,74 (t, 2H, *J*= 6,5). 5.44 (sext, 1H, *J*= 6,0). 7.49 (d, 1H. *J*= 7,0), 7,61 (t. 1H, *J*= 7,0), 8,07 (d, 1H. *J*= 7.0), 10.13 (s. 1H).

11.) 1-(2-Cianoetil)-4-(3-cianopropil)-1*H*-1,2,4-triazolium bromid

1,22 g 1*H*-1,2,4-triazol-1-propánsavnitrilből és 1,48 g 4-brómbutironitrilből a 9.) pont szerint eljárva, kitermelés 2,05 g (76 %). o.p. 104-105.5 °C. ^{1}H NMR(DMSO-d_6): 2.20 (quint. 2H), 2.66 (t. 2H), 3,21 (t, 2H), 4.39 (t, 2H). 4.63 (t. 2H). 9,35 (s. 1H). 10.28 (s, 1H).

12.) 1-(2-Cianoetil)-3-(fenilmetil)-4-fenil-1*H*-imidazolium bromid

1.) példa termék 1,97 g. benzilbromid 1,71 g 5 ml acetonitrilben visszacsepegő hűtő alatt forralva 50 órát, lehűtve, éterrel hígítva szűrjük. Kitermelés: 3,49 g (95%), o.p.173-174°C (acetonitril). ^{1}H NMR(DMSO-d_6): 3,30 (t, 2H. *J*= 6.1), 4,60 (t. 2H. *J*= 6,1). 5,55 (s, 2H). 7,05-7,14 (m, 2H). 7.31 (m. 3H). 7.50 (m, 5H). 8.10 (d. 1H, *J*= 1,3). 9,47 (d, 1H. *J*= 1,3).

13.) 1-(2-Ciano-1-metil-etil)-3-(fenilmetil)-4-metil-1*H*-benzimidazolium bromid

1.99 g 3.) pont termékéből és 1.71 g benzilbromidból a 12.) pont szerint (reakcióidő 20 óra), 3,55 g (96 %). o.p. 214-215 °C (acetonitril). ^{1}H NMR(DMSO-d_6): 1,85 (d. 3H, *J*= 6,7), 2.49 (s. 3H). 3.50 (d. 2H. *J*= 6.2). 5.51 (sext. 1H. *J*= 6.2), 6.01 (s, 2H). 7.18-7,30 (m. 2H), 7.35-7.50 (m. 4H). 7.62 (t. 1H. *J*= 7.8). 8.13 (d. 1H. *J*= 7.8). 10.30 (s. 1H).

14.) 1-(2-Cianoetil)-4-(fenilmetil)-1*H*-1,2,4-triazolium bromid

1,22 g 1H-1,2,4-triazol-1-propánsavnitrilből és 1,71 g benzilbromidból a 12.) pont szerint eljárva, kitermelés 2,38 g (81 %), o.p. 166,5-168 °C. ^{1}H NMR(DMSO-d_6): 3,23 (t, 2H), 4,71 (t, 2H), 5,57 (s, 2H), 7,40-7,54 (m, 5H), 9,43 (s, 1H), 10,28 (s, 1H).

15.) 1-(2-(Etoxikarbonil)etil)-4-(fenilmetil)-1*H*-1,2,4-triazolium bromid

4,23 g 5.) pont termékéből és 4,28 g benzilbromidból a 12.) pont szerint, kitermelés 7,28 g (85 %), o.p. 116-117 °C. ^{1}H NMR(DMSO-d_6): 1,17 (t, 3H), 3,05 (t, 2H), 4,10 (q, 2H), 4,67 (t, 2H), 5,63 (s, 2H), 7,42-7,61 (m, 5H), 9,46 (s, 1H), 10,42 (s, 1H).

16.) 1-(2-Ciano-1-metil-etil)-3-(2-propenil)-4-metil-1*H*-benzimidazolium bromid

1,99 g 3.) pont termékéből és 1,3 g allilbromidból a 12.) pont szerint, kitermelés 2,88g (90 %), o.p. 180-182 °C (acetonitril). ^{1}H NMR(DMSO-d_6): 1,78 (d, 3H, J= 7,1), 2,74 (s, 3H), 3,42 (d, 2H, J= 7,1), 5,01 (m, 1H), 5,30-5,54 (m, 2H+1H), 6,16-6,40 (m, 1H), 7,47 (d, 1H, J= 7,5), 7,61 (t, 1H, J= 7,5), 8,07 (d, 1H, J= 7,5), 10,06 (s, 1H).

17.) 1-(2-Cianoetil)-3-(((((4-metoxikarbonil)fenil)amino)karbonil)metil)-4-fenil-1*H*-imidazolium bromid

1,97 g 1.) pont termékét és 2,72 g 2-bróm-N-((4-metoxikarbonil)fenil)acetamidot 10 ml acetonitrilben visszacsepegő hűtő alatt forraljuk, lehűtjük, acetonnal hígítjuk, szűrjük, mossuk, szárítjuk. Kitermelés: 4,41 g (94 %), o.p. 205-207 °C (MeOH). ^{1}H NMR(DMSO-d_6): 3,32 (t, 2H, J= 6,9), 3,82 (s, 3H), 4,68 (t, 3H, J= 6,9), 5,28 (s, 2H), 7,55-7,60 (m, 5H), 7,63 (m, 2H), 7,94 (m, 2H), 8,11 (d, 1H, J= 1,2), 9,58 (d, 1H, J= 1,2), 10,84 (s, NH).

18.) 1-(2-Ciano-1-metil-etil)-3-(((((4-metoxikarbonil)fenil)amino)karbonil)metil)-4-metil -1*H*-benzimidazolium bromid

1,99 g 3.) pont termékéből és 2,72 g 2-bróm-N-((4-metoxikarbonil)fenil)acetamidból a 17.) pont szerint, 4,48 g (95 %), o.p. 141-143 °C (MeOH). ^{1}H NMR(DMSO-d_6): 1,39 (d, 3H, J= 7,2), 2,67 (s, 3H), 3,43 (d, 2H, J= 7,2), 3,82 (s, 3H), 5,49 (sext, 1H, J= 7,2), 5,72 (s, 2H), 7,48 (d, 1H, J= 7,1), 7,64 (t, 1H, J= 7,1), 7,76 (m, 2H), 7,98 (m, 2H), 8,10 (d, 1H, J= 7,1), 10,05 (s, 1H), 11,17 (s, NH).

19.) 1-(2-Cianoetil)-4-(((((4-metoxikarbonil)fenil)amino)karbonil)metil)-1*H*-1,2,4-triazolium bromid

1,22 g 1H-1,2,4-triazol-1-propánsavnitrilből és 2,72 g 2-bróm-N-((4-metoxikarbonil)fenil)acetamidból a 17.) pont szerint (1 óra), 3,66 g (93 %), o.p. 227-228 °C (MeOH). ^{1}H NMR(DMSO-d_6): 3,28 (t, 2H), 3,84 (s, 3H), 4,83 (t, 2H), 5,42 (s, 2H), 7,74 (d, 2H), 7,98 (d, 2H), 9,30 (s, 1H), 10,22 (s, 1H), 11,01 (s, NH).

20.) 4-(2-Cianoetil)-1-(((((4-metoxikarbonil)fenil)amino)karbonil)metil)-1*H*-1,2,4-triazolium bromid

0,30 g 4H-1,2,4-triazol-4-propánsavnitrilből és 0,67 g 2-bróm-N-((4-metoxikarbonil)fenil)acetamidból a 17.) pont szerint, kitermelés 0,41 g (42 %), o.p. 206-208 °C (MeOH).

^1H NMR(DMSO-d_6): 3.32 (t, 2H), 3,84 (s, 3H), 4.73 (t. 2H), 5,59 (s. 2H), 7,74 (d. 2H), 7,97 (d, 2H), 9.41 (s. 1H), 10,34 (s, 1H), 11:10 (s. NH).

21.) 5-Fenil-N-((4-metoxikarbonil)fenil)-1*H*-imidazol-1-acetamid

2,35 g 17.) pont termékét 5 ml 2M-os metanolos NaOMe oldattal szobahőfokon kevertetjük 5 percig, hűtjük, vizes ammónium-klorid oldattal kezeljük, 2 órát kevertetjük, szűrjük, vízzel, majd hideg acetonnal mossuk és szárítjuk. Kitermelés: 1,61 g (96 %), o.p. 220-222 °C (metanol/víz). ^1H NMR (DMSO-d_6): 3,89 (s, 3H), 4,82 (s. 2H), 7,18 (d. 1H, *J*= 1,1), 7,30-7,45 (m, 5H), 7,51 (m, 2H), 7,67 (d, 1H, *J*= 1,1), 7,99 (m, 2H + NH).

22.) 7-Metil-N-((4-metoxikarbonil)fenil)-1*H*-benzimidazol-1-acetamid

2,36 g 18.) pont termékét a 21.) pont szerint kezelve: kitermelés 1.57 g (97 %). o.p. 242-244°C (MeOH/víz). ^1H NMR (DMSO-d_6): 2,65 (s. 3H), 3,88 (s, 3H), 5,15 (s, 2H), 7,08 (d,1H, *J*= 7,4), 7,19 (t,1H, *J*= 7,4), 7.49-7.68 (m. 2H+1H +1H), 7,96 (m. 2H), 8,61 (s, NH).

23.) N-((4-Metoxikarbonil)fenil)-4*H*-1,2,4-triazol-4-acetamid

1,97 g 19.) pont termékét a 21.) pont szerint kezelve: kitermelés 1.19 g (91 %), o.p. 280-282 °C (MeOH). ^1H NMR(DMSO-d_6): 3.82 (s, 3H), 5.07 (s, 2H), 7,72 (d. 2H), 7,95 (d, 2H), 8.49 (s, 2H), 10.74 (s. NH).

24.) N-((4-Metoxikarbonil)fenil)-1*H*-1,2,4-triazol-1-acetamid

0,4 g 20.) pont termékéből a 21.) pont alapján: kitermelés 0.22 g (85%). o.p. 218-220 °C (MeOH). ^1H NMR(DMSO-d_6): 3.83 (s. 3H), 5.19 (s, 2H), 7.72 (d, 2H), 7,95 (d, 2H), 8,01 (s, 1H), 8,56 (s, 1H), 10,76 (s, NH).

25.) 5-Fenil-1-metil-1*H*-imidazol

8 g 8.) pont termékét 8 ml 20 %-os nátrium-hidroxid oldattal szobahőfokon 1 órát kevertetjük, hűtjük, szűrjük, mossuk, szárítjuk. Kitermelés: 3.61 g (97 %), o.p. 90.5-93°C.

26.) 5-Fenil-1-(fenilmetil)-1*H*-imidazol

1.84 g 12.) pont termékét a 25.) pont szerint kezeljük: kitermelés 1.05 g (90 %). o.p. 115-117 °C. ^1H NMR($CDCl_3$): 5.15 (s. 2H), 6.96-7,07 (m. 2H), 7.14 (d. 1H. *J*= 0,9), 7,24-7,42 (m, 8H), 7.57 (d. 1H, *J*= 0,9).

27.) 1-(Fenilmetil)-7-metil-1*H*-benzimidazol

1.85 g 13.) pont termékét a 25.) pont szerint kezeljük: 0,98 g (88 %). o.p. 159-160 °C. ^1H NMR($CDCl_3$): 2.47 (s. 3H), 5.67 (s. 2H), 6.92-7.05 (m. 3H), 7.18 (t. 1H, *J*= 8.2), 7,25-7,39 (m. 3H), 7.70 (d, 1H, *J*= 8.2), 7.87 (s. 1H).

28.) 5-Fenil-1*H*-imidazol-1-butánsavnitril

A 9.) pont szerint eljárva kapott reakcióelegyet bepároljuk, a kvaterner sót 10ml 20%-os nátron lúggal szobahőfokon kevertetjük 1 órát, etilacetáttal extraháljuk, a szerves fázist 3 ×

20 ml 1N HCl oldattal extraháljuk, a vizes fázist derítjük, ammónia oldattal pH 8-9 közé állítjuk, 3×20 ml diklórmetánnal extraháljuk, a szerves fázist szárítjuk, bepároljuk. Kitermelés: 1,96g (93%), o.p. 58-59°C. ^{1}H NMR($CDCl_3$): 1,88 (quint, 2H, *J*= 7,0), 2,17 (t, 2H, *J*= 7,0), 4,19 (t, 2H, *J*= 6,9), 7,10 (d, 1H, *J*= 1,0), 7,30-7,52 (m, 5H), 7,60 (d, 1H, *J*= 1,0).

29.) 7-Metil-1*H*-benzimidazol-1-butánsavnitril

A 10.) pont szerint kapott kvaterner sót tartalmazó reakcióelegyet a 28.) pont szerint reagáltatva, feldolgozva a kitermelés 1,89 g (95 % a 3.) szerinti termékre számolva). ^{1}H NMR($CDCl_3$): 2,17 (quint, 2H, *J*= 6,7), 2,35 (t, 2H, *J*= 6,7), 2,68 (s, 3H), 4,49 (t, 2H, *J*=6,7), 7,03 (d, 1H, *J*= 8,4), 7,17 (t, 1H, *J*= 8,4), 7,65 (d, 1H, *J*= 8,4), 7,85 (s, 1H). Pikrát o.p. 199-201 °C (EtOH).

30.) 7-Metil-1-(2-propenil)-1*H*-benzimidazol

2,56 g 16.) pont szerint izolált kvaterner sót a 28.) pont szerint reagáltatva, feldolgozva, kitermelés 1,24 g (90 %). ^{1}H NMR($CDCl_3$): 2,63 (s, 3H), 4,78-4,99 (m, 3H), 5,17-5,28 (m, 1H), 5,96-6,17 (m, 1H), 7,00 (d, 1H, *J*= 7,3), 7,15 (t, 1H, *J*= 7,3), 7,65 (d, 1H, *J*= 7,3), 7,81 (s, 1H).

31.) 4-(2-Propenil)-4*H*-1,2,4-triazol oxalát

1,22 g 1*H*-1,2,4-triazol-1-propánsavnitrilt és 1,3 g allilbromidot 5 ml acetonitrilben visszacsepegő hűtő alatt forralunk 10 órát, a reakcióelegyet bepároljuk és 28.) pont szerint kezeljük. A kapott nyers terméket 10 ml acetonban oldjuk, 1,26 g (0,01 mól) oxálsav dihidrát 3 ml EtOH-val készült oldatával kezeljük, hűtjük, szűrjük, acetonnal mossuk, szárítjuk. Kitermelés: 1,39 g (73%), o.p. 97-99°C. Bázis: f.p.$_3$:167-170°C.

32.) 4-(Fenilmetil)-4*H*-1,2,4-triazol

3,40 g 15.) pont termékét 1 g NaOH 30 ml metanollal készült oldatában visszacsepegő hűtő alatt forraljuk 0,5 órát. Visszahűlés után a reakcióelegyet 8 g szilikagéllel kevertetjük 0,5 órát szobahőfokon, szűrjük és bepároljuk. Az nyersterméket felvesszük 30 ml kloroformban, 5 g szilikagéllel és 2 g derítőszénnel kevertetjük 0,5 órát, szűrjük, a szűrletet bepároljuk. Kitermelés: 1,46 g (92,%), éter-hexán elegyből átkristályosítva: 113-114 °C.

33.) 4*H*-1,2,4-Triazol-4-butánsavnitril

1,69 g 5.) pont termékét és 1,48 g 4-brómbutironitrilt 5 ml nitrometánban visszacsepegő hűtő alatt forralunk 22 órát. Bepároljuk, a kvaterner sót a 32.) pont szerint kezeljük, a nyersterméket 10 ml acetonban oldjuk és 1,26 g (0,01 mól) oxálsav dihidrát 3 ml etanolos oldatával kezeljük, szűrjük, acetonnal mossuk. Kitermelés: 1,45 g (64%), o.p. 93-95°C (aceton). Bázis: ^{1}H NMR($CDCl_3$): 2,20 (quint, 2H), 2,43 (t, 2H), 4,26 (t, 2H), 8,23 (s, 2H).

34.) 1-Metil-1*H*-imidazol

68,08 g imidazolt, 105 g etilakrilátot, 1,39 g TBD-t 100 ml acetonitrilben 1 órát kevertetjük. 130 g dimetilszulfátot csepegtetünk be 0,5 óra alatt, 1 órán át visszacsepegő hűtő alatt forraljuk. A reakcióelegyet bepároljuk, 200 ml vízben oldjuk, 100 g nátrium-hidroxid és

100 ml víz elegyével kezeljük. Egy órát kevertetjük szobahőfokon, majd 5×100 ml etilacetáttal extraháljuk, a szerves fázist szárítjuk, bepároljuk, a maradékot desztilláljuk. Kitermelés: 72,2 g (88 %), f.p. 195-197 °C.

35.) 1-(Fenilmetil)-1*H*-benzimidazol

11,8 g benzimidazolt, 1,1 g etilakrilátot és 0,14 g TBD-t 30 ml acetonitrilben visszacsepegő hűtő alatt forralunk 1 órát, majd 13 g benzilkloridot adunk hozzá és további 20 órán át forraljuk. Az oldószert ledesztilláljuk, a párlási maradékot 50 ml vízben felvesszük és 10 g NaOH és 15 ml víz elegyével kezeljük. 1 órán át szobahőfokon, majd 2 órát 0-4°C között kevertetjük, a kivált terméket szűrjük, vízzel mossuk és szárítjuk. Kitermelés: 14,9 g (71 %), o.p. 116-118 °C.

36.) 1-Etil-5-fenil-1*H*-imidazol

5 g 4-fenilimidazolt, 3,7 g etilakrilátot és 0,14 g TBD-t 20 ml acetonitrilben kevertetünk 1 órát, majd 5,6 g dietilszulfátot adunk hozzá és visszacsepegő hűtő alatt 20 órán keresztül forraljuk, majd bepároljuk. A párlási maradékot 50 ml vízbe felvesszük és 3,2 g nátrium-hidroxiddal kezeljük szobahőfokon. 1 óra kevertetés után a reakcióelegyet 2×30 ml etilacetáttal extraháljuk, az egyesített szerves fázist szárítjuk, bepároljuk. Kitermelés: 5,4 g (89%) termék, f.p. 109-110 °C (0,4 Hgmm).

37.) 5-Fenil-1-(2-propenil)-1*H*-imidazol

A 36.) példával analóg módon, 2,88 g 4-fenilimidazolból, 2,2 g etilakrilátból, 0,07 g TBD-ből és 3,6 g allilbromidból kiindulva 3,17 g (86%) terméket nyerünk. ^{1}H NMR ($CDCl_3$): 4,52-4,61 (m, 2H), 4,97-5,30 (m, 2H), 5,83-6,05 (m, 1H), 7,11 (d, 1H, *J*= 1,1), 7,34-7,46 (m, 5H), 7,57 (d, 1H, *J*= 1,1). Pikrát o.p. 127-128 °C (etanol).

38.) 4-(2-Propenil)-4*H*-1,2,4-triazol oxalát

3,45 g 1,2,4-triazolt, 4 ml akrilnitrilt és 0,14 g TBD-t 10 ml acetonitrilben kevertetünk 3 órát, majd hozzáadunk 10 g allilbromidot, 4 órán keresztül visszacsepegő hűtő alatt forraljuk, majd bepároljuk. A párlási maradékot a 36.) példánál leírtak szerint kezeljük, a nyersterméket 50 ml acetonban oldjuk és 6,3 g oxálsav dihidrát 15 ml etanollal készült forró oldatával kezeljük. Hűtjük kevertetjük 4 órát, szűrjük és acetonnal mossuk. Kitermelés: 6,33 g (64 %) izomertiszta fehér kristályos termék, o.p. 97-99 °C.

39.) 4-Butil-4*H*-1,2,4-triazol oxalát

6,76 g nyers 1*H*-1,2,4-triazol-1-propánsav etilésztert 20 ml butilbromidot, 0,30 g nátrium-jodidot 20 ml nitrometánban visszacsepegő hűtő alatt forralunk 22 órát. Bepároljuk, a kvaterner sót 38.) pont szerint átalakítva. Kitermelés: 4,98 g (58 %) o.p. 109-111 °C. Bázis ^{1}H NMR($CDCl_3$): 0,95 (t, 3H), 1,36 (sext, 2H), 1,80 (quint, 2H), 4,02 (t, 2H), 8,16 (s, 2H).

40.) 4-(2-Butil)-4*H*-1,2,4-triazol

1,22 g nyers 1*H*-1,2,4-triazol-1-propánsavnitrilt 5,4 ml 2-bróm-butánt és 0,15 g nátrium-jodidot 5 ml nitrometánban visszacsepegő hűtő alatt forralunk 60 órát, majd bepároljuk. A maradékot a 36.) pont szerint kezeljük, a nyersterméket oszlopkromatográfiásan tisztítjuk, aceton:metanol 9:1 (v/v) eleggyel eluálva. Kitermelés: 0,58 g (47 %).
^{1}H NMR($CDCl_3$): 0,83 (t, 3H), 1,48 (d, 3H), 1,77 (quint, 2H), 4,15 (sext, 1H), 8,13 (s, 2H).

41.) 1-(Fenilmetil)-1*H*-imidazol-5-karbonsav etilészter

1,26 g imidazol-4-karbonsav metilésztert, 1g krotonsavnitrilt és 0,03 g TBD-t visszacsepegő hűtő alatt forralunk 1 órát, majd 1,71 g benzilbromidot adunk hozzá és további 60 órát forraljuk, majd bepároljuk. A párlási maradékot felvesszük 10 ml 2M-os etanolos Na-etilátban, 10'-et szobahőfokon, majd 20'-et 60 °C-on kevertetjük, lehűtjük, 20 ml 10 %-os ammóniumklorid oldattal kezeljük, 20 órát ezen a hőfokon kevertetjük, szűrjük, hideg vízzel mossuk, szárítjuk. Kitermelés: 1,82 g (79 %), o.p. 64-65°C.

42.) 1-Metil-1*H*-imidazol-5-karbonsav etilészter

1,26 g imidazol-4-karbonsav metilésztert, 1g krotonsavnitrilt és 0,03 g TBD-t visszacsepegő hűtő alatt forralunk 1 órát, majd 1,05 ml (1,38 g) dimetil-szulfátot adunk hozzá, további 3 órát forraljuk, bepároljuk. A maradékot felvesszük 10 ml 2M-os etanolos nátrium-etilát oldatban, 60'-et szobahőfokon kevertetjük, lehűtjük, 20ml 10%-os ammónium-klorid oldattal kezeljük, 20 órát kevertetjük, szűrjük, mossuk. Kitermelés: 1,05g (75%), o.p. 54-56°C.

43.) 4-Nitro-1-(3-oxobutil)-1*H*-imidazol

2,26 g 4-nitroimidazolt, 2 ml (1,71 g) metil-vinil ketont és 0,14 g TBD-t 25 ml acetonitrilben visszacsepegő hűtő alatt forralunk 1 órát, majd bepároljuk. A párlási maradékot 10 ml 10 %-os ammóniumklorid oldattal kezeljük, hűtjük, szűrjük, vízzel mossuk. Kitermelés: 3,41 g (93 %), o.p. 73-74,5 °C (EtOAc). ^{1}H NMR($CDCl_3$): 2,10 (s, 3H), 3,11 (t, 2H), 4,22 (t, 2H), 7,83 (d, 1H), 8,36 (d, 1H).

44.) 7*H*-Teofillin-7-propánsavnitril

3,6 g teofillint és 0,14 g TBD-t 15 ml akrilnitrilben kevertetünk 120 órát, bepároljuk, a nyersterméket a 43.) pont szerint kezeljük. Kitermelés: 4,43 g (95 %), o.p. 159-161 °C, EtOAc-ból kristályosítva: o.p. 160-161 °C.

45.) 3-Fenil-1*H*-1,2,4-triazol-1-propánsavnitril

2,90 g 3-fenil-1*H*-1,2,4-triazolból a 44.) pont szerint: kitermelés 3,65 g (92%), o.p. 86,5-88°C. ^{1}H NMR($CDCl_3$): 3,04 (t, 2H), 4,45 (t, 2H), 7,37-7,52 (m, 3H), 8,02-8,15 (m, 2H), 8,20 (s, 1H).

46.) 3-Fenil-1*H*-pirazol-1-propánsavnitril

2,88 g 3-fenilpirazolból a 44.) pont szerint: kitermelés 3,43 g (87%), o.p. 51-53°C (éter-hexán). ^{1}H-NMR ($CDCl_3$): 3,00 (t, 2H), 4,42 (t, 2H), 6,58 (d, 1H), 7,30-7,48 (m, 3H), 7,52 (d, 1H), 7,78 (m, 2H).

47) 1*H*-Benztriazol-1-propánsavnitril és 2*H*-benztriazol-2-propánsavnitril

2,38 g benztriazolból a 44.) pont szerint eljárva. A nyersterméket kromatográfiásan tisztítva (eluens kloroform : aceton 95:5), kitermelés 2,26 g (66 %), o.p. 78-80 °C.

48.) 1-Metil-5-nitro-1*H*-imidazol

a) 2,26 g 4-nitroimidazolt, 1,6 ml akrilnitrilt és 0,07 g TBD-t 10 ml acetonitrilben visszacsepegő hűtő alatt forralunk 8 órát, 2,1 ml (2,78 g) dimetilszulfátot adunk hozzá, további 3 órát forraljuk. Az elegyet lehűtjük, becsepegtetünk 3,16 ml (3,37 g) 7-metil-1,5,7-triazabiciklo[4.4.0]dec-5-ént (7-Me-TBD-t). 0,5 órát szobahőfokon kevertetjük, bepároljuk szilikagéllel töltött oszlopon etilacetát : aceton (2:1) eleggyel eluáljuk. Kitermelés: 1,45 g (57 %), o.p. 52-54 °C.

b) 1,45 g 4-nitro-1-(3-oxobutil)-1*H*-imidazolt és 0,76 ml (1,01 g) dimetilszulfátot 5 ml acetonitrilben forralunk visszacsepegő hűtő alatt 4 órát. Lehűtjük, kevertetés mellett 2,76 g porított káliumkarbonátot adunk be. Szobahőfokon kevertetjük 10 órát, szűrjük, bepároljuk, az a) pontnál leírtak szerint kromatografáljuk. Kitermelés: 0,87 g (87 %), o.p. 53-55 °C.

49.) 7-(3-Oxobutil)-7*H*-teofillin

5,4 g teofillint, 2,7 ml (2,31 g) metil-vinil-ketont és 0,14 g TBD-t 20 ml acetonitrilben visszacsepegő hűtő alatt forralunk 3 órát. Bepároljuk, a maradékot 40 ml 10%-os HCl oldatban felvesszük, 60-70°C-on derítjük. A szűrletet hűtjük, kémhatását 25 %-os ammóniaoldattal pH 8-ra állítjuk. Kristályosítjuk 0-4 °C-on, szűrjük, mossuk. Kitermelés: 6,31 g (84 %), o.p. 138,5-140 °C (etilacetát).

50.) 5-Metil-5*H*-imidazo[4,5-c]piridin oxalát

1,19 g 5-azabenzimidazolt, 1 ml (0,8 g) akrilnitrilt és 0,014 g TBD-t 5 ml acetonitrilben kevertetünk szobahőfokon 0,5 órát, majd 0,75 ml (1,7 g) metiljodidot beadva további 4 órát kevertetjük. Bepároljuk, a maradékhoz 5 ml 20 %-os nátrium-hidroxid oldatot adva 4 órát kevertetjük, telített só oldatot beadva 5×30 ml diklórmetánnal extraháljuk. A szerves fázist szárítjuk, derítjük, bepároljuk, a maradékot 10 ml acetonban oldjuk, 1,26 g oxálsav 5 ml forró etanollal készült oldatával kezeljük, hűtjük, szűrjük, acetonnal mossuk. Kitermelés: 0,98 g (44 %), o.p. 188-190 °C (EtOH).

51.) 5-(Fenilmetil)-5*H*-imidazo[4,5-c] oxalát

Az 50.) pont szerint, alkilezőszerként 1,71 g benzilbromidot alkalmazunk, a kvaternerezési idő szobahőfokon 20 óra. Kitermelés: 1,08 g (33 %), o.p. 142-143,5 °C (EtOH).

52.) β-Metil-1*H*-imidazol-1-propánsavnitril

13,6 g imidazolt, 18,5 ml (15 g) metakrilnitrilt és 0,3 g TBD-t 30 ml acetonitrilben forralunk visszacsepegő hűtő alatt 100 órát. 24 óránként 5-5 ml metakrilnitrilt adunk az

57.) 4-Acetamino-1-(2-cianoetil)-3-(fenilmetil)-imidazolium bromid

1,78 g (0,01 mól) 4-acetamino-1*H*-imidazol-1-propánsavnitrilt és 2,56 g (0,015 mól) benzil-bromidot 20 ml MeCN-ben visszacsepegő hűtő alatt forralunk 16 órát, majd lehűtjük, a kivált kristályos terméket szűrjük, acetonnal mossuk és szárítjuk. Kitermelés: 3,05 g (87 %), o.p.: 194-196 °C.

58.) 3-[*N*-acetil-*N*-(1-(fenilmetil)-1*H*-imidazol-5-il)]amino-propánsavnitril és 5-acetamino-1-(fenilmetil)-1*H*-imidazol

2,4 g (6,9 mmól) 4-Acetamino-1-(2-cianoetil)-3-(fenilmetil)-imidazolium bromidot és 2,1 ml (2,13 g, 14 mmól) diaza-biciklo-undecént (DBU-t) 10 ml MeCN-ben kevertetünk 50°C-on 0,5 órát. Bepároljuk, a párlási maradékot 15ml 10%-os ammónium-klorid oldattal kezeljük, 3-szor 20ml diklórmetánnal extraháljuk. A szerves fázist bepároljuk, a maradékot szilikagél oszlopon aceton:metanol 9:1 eleggyel eluáljuk. A kapott első frakció a 3-[*N*-acetil-*N*-(1-(fenilmetil)-1*H*-imidazol-5-il)]amino-propánsavnitril: 0,72 g, o.p.: 112-114 °C (EtOAc). ^{1}H NMR (DMSO-d_6): 1,36 (s, 3H), 2,56-2,72 (m, 2H), 2,73-2,91 (m, 1H), 4,02-4,22 (m, 1H), 5,08 (m, 2H), 6,94 (s, 1H), 7,19-7,43 (m, 5H), 7,92 (s, 1H). MS (EI$^+$, 70 eV) (m/z, %): 268 (M$^+$, 3), 226 (8), 186 (27), 91 (100). IR (KBr): 1574, 1671, 2255 cm^{-1}. A második frakció az 5-acetamino-1-(fenilmetil)-1*H*-imidazol: 0,40 g, o.p.: 149-151 °C (toluol:n-butanol 10:1). ^{1}H NMR (DMSO-d_6): 1,98 (s, 3H), 5,05 (s, 2H), 6,75 (s, 1H), 7,08-7,20 (m, 2H), 7,26-7,41 (m, 3H), 7,49 (s, 1H), 9,59 (NH). MS (EI$^+$, 70 eV) (m/z, %): 215 (M$^+$, 9), 173 (18), 91 (100).

59.) 5-Acetamino-1-(fenilmetil)-1*H*-imidazol

50 ml 2M-os metanolos MeONa oldathoz (0,1 mól MeONa) keverés mellett 2,96 g (8,5 mmól) 4-acetamino-1-(2-cianoetil)-3-(fenilmetil)-imidazolium bromidot adagolunk. Az elegyhez 5 perc múlva 4,9 g ammónium-kloridot, majd 10 g szilikagélt adunk, 0,5 órát kevertetjük. Szűrjük, a szűrletet bepároljuk, a maradékot toluol—n-butanol elegyből kristályosítjuk. Kitermelés: 1,20 g (66 %), o.p.: 150-152 °C.

60.) *E*-1-(2-cianoetil)-1*H*-imidazol-4-propénsav etilészter

3,32 g (0,02 mól) *E*-1*H*-imidazol-4-propénsav etilésztert (urokánsav etilésztert), 1,45 ml (1,17 g, 0,022 mól) akrilnitrilt és 0,14 g (1 mmól) TBD-t 8 ml MeCN-ben kevertetünk szobahőfokon 10 órát, majd −18 °C-on kristályosítjuk 24 órát, szűrjük. Kitermelés: 4,03 g (92 %), o.p.: 120-121,5 °C (EtOH). ^{1}H NMR ($CDCl_3$): 1,31 (t, 3H), 2,84 (t, 2H), 4,16-4,33 (m, 4H), 6,57 (d, 1H, *J*= 15 Hz), 7,22 (m, 1H), 7,55 (d, 1H, *J*= 15 Hz), 7,59 (m, 1H). MS (EI$^+$, 70 eV) (m/z, %): 219 (M$^+$, 27), 174 (100), 147 (46), 105 (25).

61.) 4-Nitro-1*H*-benzimidazol-1-propánsavnitril

3,1 g (19 mmól) 4-nitro-benzimidazolt, 20 ml akrilnitrilt, 2,45 g (20 mmól) 4-(dimetilamino)-piridint és 0,14 g (1 mmól) TBD-t 10 ml MeCN-ben 70°C-on 6 órát kevertetünk, majd lehűtjük, −18°C-on kristályosítjuk, szűrjük. Kitermelés: 3,8 g (88 %), o.p.: 195-196°C (aceton). ^{1}H-NMR (DMSO-d_6): 3,19 (t, 2H), 4,72 (t, 2H), 7,52 (t, 1H), 8,10 (dd, 1H), 8,25 (dd, 1H), 8,63 (s, 1H). MS (EI$^+$, 70 eV) (m/z, %): 216 (M$^+$, 100), 186 (68), 146 (33), 118 (94).

62.) α,4-Dimetil-1*H*-imidazol-1-propánsavnitril oxalát

1,64 g (0,02 mól) 4-metil-imidazolt és 1,45 ml (1,17g, 0,022 mól) akrilnitrilt 8 ml MeCN-ben kever-tetünk 80 °C hőmérsékleten 5 órát, majd bepároljuk, a párlási maradékot 5 ml acetonban oldjuk és 2,52 g (0,02 mól) oxálsav dihidrát 5 ml EtOH-val készült forró oldatával kezeljük. Lehűtjük, a kivált kristályokat szűrjük, acetonnal mossuk. Kitermelés: 3,11 g (65 %), o.p.: 104-105,5 °C (EtOH). ^{1}H NMR (DMSO-d_6): 1,51 (d, 3H, J= 6,8 Hz), 2,20 (d, 3H, J= 0,9 Hz), 3,17 (d, 2H, J= 6,6 Hz), 4,77 (sext, 1H, J= 6,7 Hz), 7,38 (m, 1H), 8,51 (d, 1H, J= 1,5 Hz). MS (EI$^+$, 70 eV) (m/z, %): 149 (bázis M$^+$, 48), 109 (100), 81 (43).

63.) *E*-1-(2-propenil)-1*H*-imidazol-5-propénsav etilészter

3,29 g (0,015 mól) *E*-1-(2-cianoetil)-1*H*-imidazol-4-propénsav etilésztert, 1,7 ml (2,43 g, 0,02 mól) allil-bromidot és 0,5 g NaI-ot 20 ml MeCN-ben kevertetünk 50 °C hőmérsékleten 120 órát. Lehűtés után 10 °C hőmérsékleten beadunk 3 ml (3,04 g, 0,02 mól) diaza-biciklo-undecént (DBU-t), majd 25 °C hőmérsékleten kevertetjük 0,5 órát és bepároljuk. A párlási maradékot 30 ml 10 %-os ammónium-klorid oldattal kezeljük, majd 3-szor 20 ml diklórmetánnal extraháljuk. A szerves fázist bepároljuk és a párlási maradékot egy rövid szilikagél oszlopon acetonnal eluáljuk. Kitermelés: 2,75 g (89 %), o.p.: 120 °C.

64.) 1-(Pivaloiloxi)metil-5-metil-1*H*-imidazol

2,39 g (0,01 mól) α,4-Dimetil-1*H*-imidazol-1-propánsavnitril oxalátot 10°C hőmérsékleten beadunk 35ml 10%-os ammóniaoldatba keverés mellett, majd a kapott elegyet 3-szor 20ml diklórmetánnal extraháljuk. A szerves fázist bepároljuk, a párlási maradékhoz 5 ml MeCN-t, 1,6 ml (1,66 g, 0,011 mól) pivalinsav klórmetilésztert és 0,2 g NaI-ot adunk, 25°C hőmérsékleten kevertetjük 10 napon át, majd 15 ml EtOAc-al higítjuk, hűtjük és szűrjük. A kapott 2,4g imidazolium sót 20ml MeCN-ben oldjuk és 10°C hőmérsékleten 1,65ml (1,67g, 0,011mól) diaza-biciklo-undecénnel (DBU-val) kezeljük, majd 25°C hőmérsékleten kevertetjük 0,5 órát. Bepároljuk, a maradékot 30ml 10%-os ammónium-klorid oldattal kezeljük, majd 3-szor 20 ml diklórmetánnal extraháljuk. A szerves fázist bepároljuk, a maradékot szilikagél oszlopon EtOAc:MeOH eleggyel kromatografáljuk. Kitermelés: 1,02 g (52 %), színtelen olaj. ^{1}H NMR ($CDCl_3$): 1,18 (s, 9H), 2,27 (d, 3H, J= 1,0 Hz), 5,80 (s, 2H), 6,78 (m, 1H), 7,61 (m, 1H). MS (EI$^+$, 70 eV) (m/z, %): 196 (M$^+$, 7), 95 (20), 94 (28), 57 (100).

65.) 5-Bróm-1-metil-1*H*-imidazol

2,94 g (0,02 mol) 4-bróm-imidazolt 1,79 ml (1,48 g, 0,022 mol) krotonsavnitrilt és 0,14 g (1 mmol) TBD-t 15 ml acetonitrilben 80 °C-on kevertetjük 3 órát, beadunk 2,1 ml (2,77g, 0,022 mol) dimetil-szulfátot, majd további 3 órát kevertetjük ezen a hőfokon. Lehűtjük 10 °C-ra, beadunk 3,3 ml (3,34 g, 0,022 mol) DBU-t, 25 °C-on fél órát kevertetjük, bepároljuk az elegyet. A maradékot 30 ml 10 %-os vizes ammónium-klorid oldattal kezeljük, 3×20 ml diklórmetánnal extraháljuk. A szerves fázist bepároljuk, a maradékot szilikagélen acetonnal eluáljuk. Kitermelés 2,74 g, 85%. Olvadáspont 44-46°C.

elegyhez. Bepároljuk, kitermelés 27,96 g. ^{1}H NMR($CDCl_3$): 1,29 (d, 3H), 3,08 (sext, 1H), 4,13 (d, 2H), 7,05 (s, 1H), 7,56 (s, 1H).

53.) 1-(2-Ftalimidoetil)-1*H*-imidazol

1,36 g imidazolt, 1,7 ml (1,32 g) akrilnitrilt és 0,03 g TBD-t 5 ml acetonitrilben visszacsepegő hűtő alatt forralunk 0,5 órát. Beadunk 5,1 g 2-brómetil-ftálimidet, további 8 órát forralva, lehűtjük, 35 ml étert adunk be, 0-5 °C-on kristályosítjuk, szűrjük. A nyers kvaterner sót 200 ml metanolban oldjuk, 2,88 ml (3,06 g) 7-Me-TBD-t adunk hozzá, 5 óra kevertetjük, bepároljuk, 20 ml 100 g/l-es ammóniumklorid oldattal kezeljük, 0-5 °C-on kevertetjük, szűrjük, mossuk és szárítjuk. Kitermelés: 4,39 g (91 %), o.p. 165-167 °C (2-propanol).

54.) 5-Fenil-1-metil-1*H*-pirazol

1,97 g 3-fenil-1*H*-pirazol-1-propánsavnitrilt, 1,05 ml (1,38 g) dimetilszulfátot 5 ml acetonitrilben visszacsepegő hűtő alatt forralunk 15 órát. 10-15 °C-on beadunk 1,58 ml (1,69 g) 7-Me-TBD-t, kevertetjük 5 órát, bepároljuk a maradékot 10 ml 100 g/l-es ammóniumklorid oldattal kezeljük. 3×20 ml kloroformmal extraháljuk. Az egyesített szerves fázist szárítjuk, derítjük, bepároljuk, a maradékot (1,37 g) desztillációval tisztítjuk, kitermelés: 0,94 g (59 %), f.p.$_{12}$ 118 °C.

55.) 3-Fenil-4-metil-4*H*-1,2,4-triazol

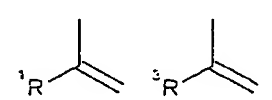
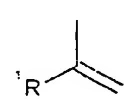
1,98 g 3-fenil-1*H*-1,2,4-triazol-1-propánsavnitrilt az 54.) példa szerint kezelünk, a nyersterméket petroléter-etilacetátból kristályosítjuk.
Kitermelés: 1,00 g (63%), o.p. 111-113°C.

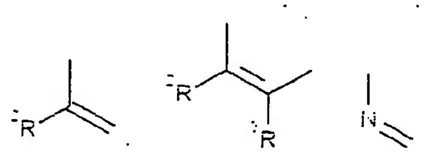
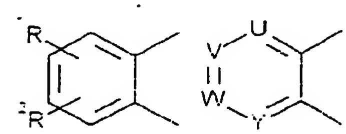
56.) 1,3,9-Trimetil-xantin (izokoffein)

1,4 g 7*H*-teofillin-7-propánsavnitrilt és 0,7 ml (0,88 g) dimetilszulfátot 5 ml acetonitrilben visszacsepegő hűtő alatt forralunk 15 órát. 10-15 °C -on beadunk 1 ml (1,07 g) 7-Me-TBD-t, szobahőmérsékleten kevertetjük, bepároljuk, beadunk 5 ml etanolt, 0-5 °C-on kevertetjük, szűrjük, hideg etanol-víz eleggyel mossuk. Kitermelés: 0,91 g (78 %), o.p. 294-295°C (EtOH-víz).

Igénypontok

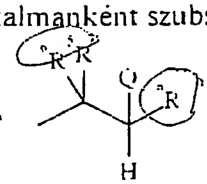
1. Eljárás legalább két nitrogén atomot tartalmazó N-alkilezett azolok előállítására [I. általános képlet

ahol A jelentése —, , B jelentése ,

D jelentése , BD jelentése 

illetve R^1, R^2, R^3 jelentése H, alkalmanként szubsztituált C_{1-4}alkil,

N

		(szubsztituált)fenil, $NHCOC_{1-4}$alkil, $COOC_{1-4}$alkil
	U, V, W, Y, Z jelentése	CH, N, CO, CS, N-C_{1-8}alkil, C-OC_{1-4}alkil, C-SC_{1-4}alkil, C-N(C_{1-4}alkil)$_2$
	n jelentése	0, 1
	X jelentése	klór-vagy bróm-vagy jód atom, C_{1-4}alkilSO_3, OSO_3R^7, C_{1-4}fluórozottalkil-SO_3, (szubsztituált)fenil-SO_3,
illetve	R^7 jelentése	-, H, alkalmanként szubsztituált C_{1-8}alkil, N-tartalmú heteroaril
nem olvasható	R^8 jelentése	-, H, 
	R^4, R^5, R^6 jelentése	H, alkil, cikloalkil, Q
illetve	Q jelentése	CN, $COOC_{1-4}$alkil, COC_{1-4}alkil, CO(szubsztituált)fenil, SO_2C_{1-4}alkil, SO_2(szubsztituált)fenil

legalább két szubsztituálatlan nitrogén atomot tartalmazó azolok [2. általános képlet, ahol A, B, D jelentése a fenti] és elektronszívó csoporttal szubsztituált olefinek [3. általános képlet; R^4, R^5, R^6 jelentése a fenti] reakciójában *azzal jellemezve, hogy*

a.) a reakciót a bázisként és/vagy transzfer reagensként funkcionáló szubsztituált amidin [4. általános képlet, ahol E, J, L jelentése —, H, alifás gyűrű maradék, N-tartalmú alifás gyűrű maradék] katalizátor jelenlétében játszatjuk le.

b.) a kapott N-monoalkilazol [5. általános képlet, ahol A, B, D, R^4, R^5, R^6 jelentése a fenti] alkalmanként alkáli-halid katalizátor jelenlétében valamely alkilezőszer [6. általános képlet, ahol X és R^7 jelentése a fenti] reakciójában képződött kvaterner azólium só [7. általános képlet, ahol A, B, D, Q, X, R^4, R^5, R^6, R^7 jelentése a fenti] a Q-elektronszívó csoportot tartalmazó (szubsztituált)etil szubsztituenst alkalmasan megválasztott bázissal szelektíven lehasítjuk.

2. Eljárás az 1/a. igénypont szerint *azzal jellemezve, hogy* bázikus katalizátorként célszerűen 1,5,7-triazabiciklo[4.4.0]dec-5-ént vagy 7-metil-1,5,7-triazabiciklo[4.4.0]dec-5-ént alkalmazunk önmagukban vagy polimer hordozóra felvive.

3. Eljárás az 1/a, 2 igénypont szerint *azzal jellemezve, hogy* az etilén származékot célszerűen mol feleslegben, esetenként oldószerként alkalmazzuk.

4. Eljárás az 1/a, 2, 3 igénypont szerint *azzal jellemezve, hogy* a terméket az elegy bepárlásával vagy vizzel, vizes szervetlen só, célszerűen ammonium-klorid vagy ammónium-karbonát oldattal kezelve szűréssel izoláljuk.

5. Eljárás az 1/b igénypont szerint *azzal jellemezve, hogy* a Michael adduktot [5. általános képlet] 0,9-10, célszerűen 1-5 ekvivalens alkilezőszerrel, esetenként izolálás nélkül, in situ reagáltatjuk.

6. Eljárás az 1/b, 5 igénypontok szerint *azzal jellemezve, hogy* a képződött azólium sót [7. általános képlet] a reakcióelegy bepárlásával vagy aprotikus oldószerrel higítva szűréssel izoláljuk.

7. Eljárás az 1/b, 5, 6 igénypontok szerint *azzal jellemezve, hogy* az azólium sót izolálás nélkül vagy izolálva alkoholos és/vagy vizes oldatban 0-100°C-on, 0,95-5 ekvivalens bázissal kezeljük.

8. Eljárás az 1/b, 5-7 igénypontok szerint *azzal jellemezve, hogy* a terméket az elegy bepárlásával, vagy vízzel, vizes szervetlen só, célszerűen ammónium-klorid vagy ammónium-karbonát oldattal kezelve szűréssel izoláljuk.

9. Eljárás az 1/b, 5-8 igénypontok szerint *azzal jellemezve, hogy* az elegyet bepárolva, a maradékot vízzel elkeverve, vízzel nem elegyedő szerves oldószerrel extrahálva izoláljuk a terméket.

10. Eljárás az 1-9 igénypont szerint *azzal jellemezve, hogy* a Michael-addíciót és/vagy alkilezést poláros-aprotikus oldószerben, célszerűen acetonitrilt vagy nitrometánt alkalmazva 0-150°C-on, célszerűen 20-120°C-on vezetjük.

Horváth András
Salamon Vilmos

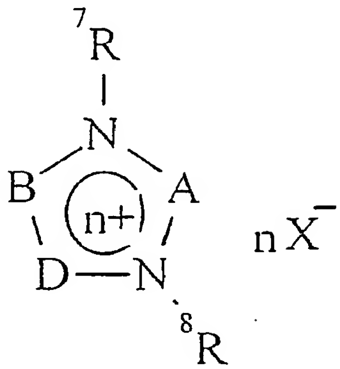
+1 lap rajz

P9500962

1/1

Ábrák

KÖZZÉTÉTELI PÉLDÁNY



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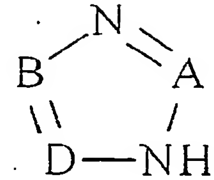

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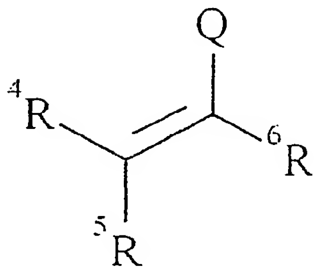

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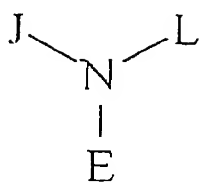

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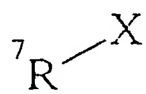

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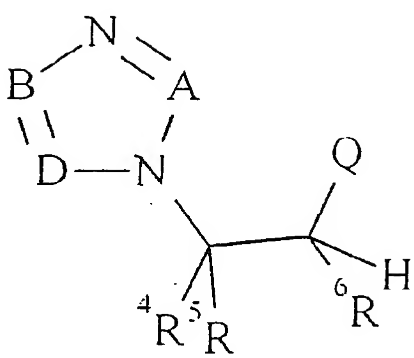

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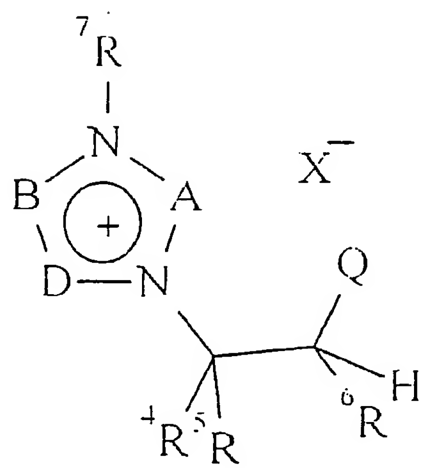

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Lapsed

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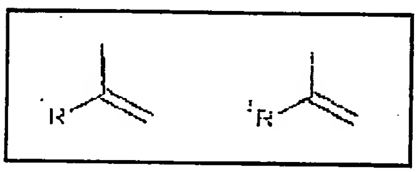

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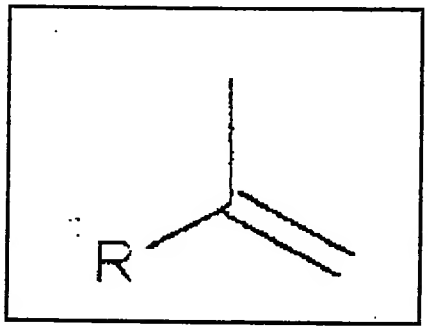

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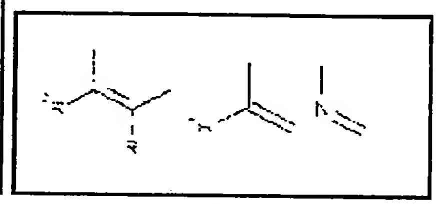

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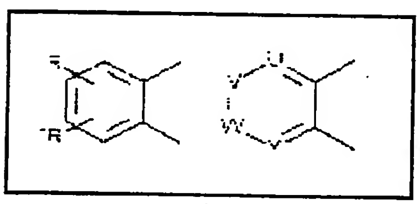

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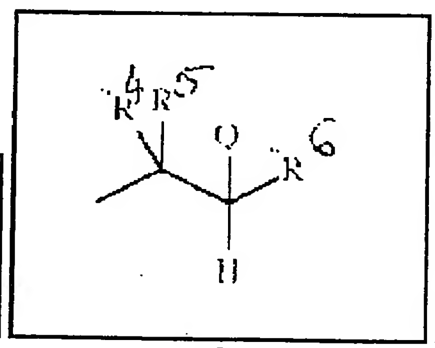

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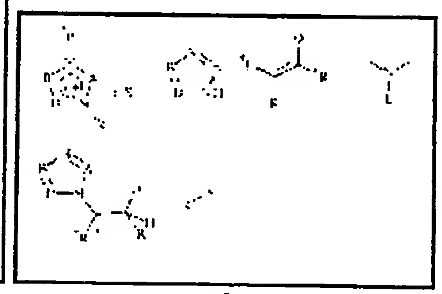

6

Abstract (first publication):

A találmány tárgya eljárás (1) általános képletű azolok előállítására a képletben

A jelentése

B jelentése

D jelentése

BD jelentése

R^1, R^2, R^3 jelentése H adott esetben szubsztituált C_{1-4}alkil, (szubsztituált) fenil, NHCOC$_{1-4}$ alkil, COOC$_{1-4}$alkil, U,V,W,Y,Z jelentése CH, N, CO, CS, NC$_{1-8}$alkil, COC$_{1-4}$alkil, CSC$_{1-4}$alkil, CN(C$_{1-4}$alkil)$_2$, n jelentése 0,1m X jelentése klór- vagy bróm- vagy jódatom, C$_{1-4}$alkil SO_3, OSO_3R^7, C$_{1-4}$fluorozott alkil- SO3, (szubsztituált)fenil-SO_3, R^7 jelentése - H adott esetben szubsztituált C$_{1-8}$alkil N-tartalmú hetoroaril, R^8 jelentése- H, R^4, R^5, R^6 jelentése H, alkil, cikloalkil, Q, Q jelentése CN, COOC$_{1-4}$alkil COC$_{1-4}$alkil, CO(szubsztituált)fenil, SO_2C_{1-4}alkil, SO_2(szubsztituált)fenil.

Az eljárás szerint eljárva a legalább két N-atomot tartalmazó N-szubsztituálatlan azolt (2.

általános képlet) szerves amidin jellegű katalizátor (4. általános képlet, ahol E. J.L jelentése H alifás gyűrű maradék, N-tartalmú alifás gyűrű maradék), poláros-aprotikus oldószer(ek)ben reagáltatják, Q elektronszívó csoporttal szubsztituált etilén származékokkal (3. általános képlet), míg B) eljárás szerint eljárva az N-monoszubsztituált-azolt (5. képlet) poláros oldószerben halogenidionos katalizátort beadva, alkilezőszer-rel (6. általános képlet) majd bázissal reagáltatva kapják a terméket (1. általános képlet (n=0, R^8=—).

Measures

0. Data publication (A0)
Measure Date: 1995.04.04 *Announcement:* 1995.05.29 (AA1A Communication of patent application data)

5. Publication of patent application (CV)
Measure Date: 1999.03.30 *Announcement:* 1999.05.28 (BB9A Publication of patent applications)

8. Lapse of provisional patent protection due to non-payment of fees (EF)
Measure Date: 2000.01.13 *Reception:* 2000.01.19 *Announcement:* 2000.02.28 (FD9A Lapse of provisional patent protection due to non-payment of fees)

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(51) INT CL^5
C07D 471/04, A61K 31/44 // (C07D 471/04 213:72 233:54)

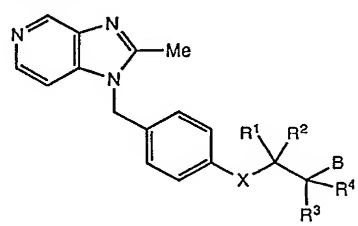
(52) UK CL (Edition L)
C2C CAA CQN CQT CRA CRE CUL C1173 C1175 C1390 C1420 C1432 C1470 C1510 C1530 C200 C213 C214 C215 C22Y C220 C225 C226 C227 C246 C25Y C250 C251 C252 C253 C254 C255 C256 C28X C30Y C31Y C311 C314 C339 C34Y C340 C342 C35Y C351 C355 C36Y C364 C366 C368 C387 C396 C43X C440 C463 C464 C551 C552 C604 C613 C62X C624 C625 C627 C628 C65X C652 C658 C665 C697 C699 C70Y C80Y C802
U1S S1318 S1321 S2414 S2415 S2416

(56) Documents cited
WO 91/17157 A

(58) Field of search
UK CL (Edition L) C2C CQN CQT CRA CRE CUL
INT CL^5 C07D
Online database: CAS ONLINE

(54) 1H-2-Methylimidazo(4,5-c)pyridinyl derivatives as PAF antagonists

(57) Compounds of general formula I;



I

wherein:

X represents a –C(=O)–, –C(=S)–, –S(–>O)– or –S(=O)$_2$– group;

R^1, R^2, R^3, and R^4 each independently represents hydrogen or one of various defined substituents or any combination of R^1, R^2, R^3 and R^4 together with the atoms to which they are attached form a 5 to 8 membered heterocyclic ring;

or any combination of R^1, R^2, R^3, and R^4 together with the carbon atom to which they are attached form a C_3-C_8 cycloalkyl ring;

B represents a) a –$(CH_2)_m$A group wherein m is 0 or 1 and the group A represents a 5- or 6-membered heterocyclic ring, which heterocyclic ring may be optionally fused to a benzene ring or to a further 5-, 6- or 7- membered heterocyclic ring containing one or more nitrogen atoms, wherein at least one of the said heterocyclic rings may also contain an oxygen or sulphur atom, and wherein any of the rings may be optionally substituted with one or more of certain defined substituents,

b) a ZR^8 group wherein Z is –C(=O)–, –C(=O)O–, –C(=O)S–, –CH_2O–, –CH_2OC(=O)–, –C(=S)–, –C(=S)O–, –CH_2S–, –CH_2OC(=O)C (=O)O–, –CH_2OSO_2–, –NHC(=O)O–, –CH_2OC(=O)NH– or –CH_2C(=O)O– group and R^8 is hydrogen or one of certain defined organic groups.

(continued overleaf)

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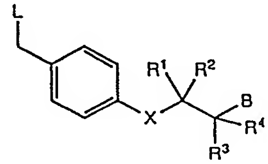
(57) (continued)

c) a $-CH_2NR^9R^{10}$ group or a $-CONR^9R^{10}$ group wherein each of R^9 and R^{10} is independently hydrogen, $-C_1-C_6$ alkyl, $-C_3-C_8$ cycloalkyl, pyridinyl, a group D or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring; D being a defined aryl or aralkyl group,

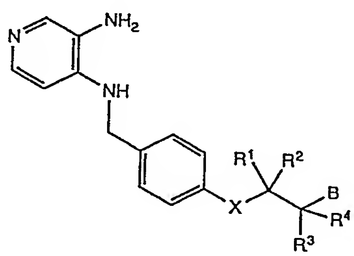
and their pharmaceutically and veterinarily acceptable acid addition salts and hydrates are *antagonists of platelet activating factor (PAF)* and as such are useful in the *treatment or amelioriation of various diseases or disorders mediated by PAF.*

Precursors of the above compounds have the formulae:-



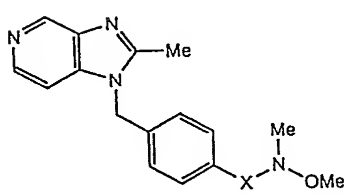
II

wherein L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy,



III

and



IV

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1H-2-Methylimidazo[4,5-c]pyridinyl derivatives as PAF antagonists

This invention relates primarily to novel compounds which are antagonists of platelet activating factor.

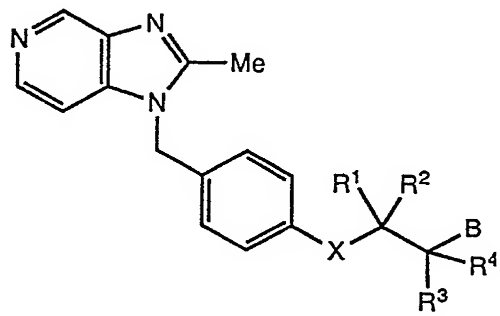
Platelet Activating Factor (PAF) is a bioactive phospholipid which has been identified as 1-*O*-hexadecyl/octadecyl-2-acetyl-*sn*-glyceryl-3-phosphoryl choline. PAF is released directly from cell membranes and mediates a range of potent and specific effects on target cells resulting in a variety of physiological responses which include hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, and increased vascular permeability (oedema/erythema). It is known that these physiological effects occur in many inflammatory and allergic diseases and PAF has been found to be involved in a number of such conditions including asthma, endotoxin shock, glomerulonephritis, immune regulation, transplant rejection, gastric ulceration, psoriasis, embryo implantation and cerebral, myocardial and renal ischemia. Thus the compounds of the invention, by virtue of their ability to antagonise the actions of PAF, should be of value in the treatment of any of the above conditions.

Compounds that have been disclosed as possessing activity as PAF antagonists include compounds which are structurally related to the PAF molecule such as glycerol derivatives (EP-A-0238202), and heterocyclic compounds such as 5-oxy derivatives of tetrahydrofuran (US-4,888,337) and 2,5-diaryl tetrahydrofurans (EP-A-0144804). Recently a more potent 2,5-diaryl tetrahydrofuran derivative, (*trans*)-2-(3-methoxy-5-methylsulphonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (L-659,989) has been disclosed (EP-A-0199324). In our International patent application No. WO 91/17157 we disclose a series of γ-butyrolactol derivatives as PAF antagonists. The compounds of WO 91/17157 differ from the 5-oxy derivatives of tetrahydofuran described in US-4,888,337 and from the 2,5-diaryl tetrahydrofurans such as L-659,989, in that they feature an appended heterocycle with an unsubstituted sp^2 nitrogen atom. There are a number of other PAF antagonists, in addition to those of WO 91/17157, for which the presence of a heterocyclic sp^2 nitrogen atom appears to be an important requirement for activity (Whittaker, M., Curr. Opin. Thera. Patents 2(5), 583-623 (1992)).

For the compounds of the present invention the presence of a heterocyclic group

possessing an unsubstituted sp^2 nitrogen atom is also a requirement for PAF antagonist activity. However, the present invention provides novel and useful substituted phenyl sulphonyl and phenylcarbonyl derivatives and their pharmaceutically acceptable acid addition salts, and pharmaceutical uses thereof as PAF antagonists.

According to a first aspect of the invention there is provided a compound of general formula I;

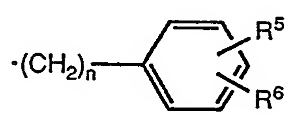


I

wherein:

X represents a -C(=O)-, -C(=S)-, -S(→O)- or -S(=O)$_2$- group;

R^1, R^2, R^3, and R^4 each independently represents hydrogen, -C_1-C_6 alkyl optionally substituted by one or more halogen atoms, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl, -(C_1-C_6 alkyl)SC_1-C_6 alkyl, -(C_1-C_6 alkyl)OC_1-C_6 alkyl, -(C_1-C_6 alkyl)N(C_1-C_6 alkyl)$_2$, -C_3-C_8 cycloalkyl, -C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)C_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)OC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)OC_4-C_8 cycloalkenyl, -(C_1-C_6 alkyl)SC_3-C_8 cycloalkyl, -(C_1-C_6 alkyl)SC_4-C_8 cycloalkenyl, a side chain of a naturally occurring amino acid or a group D wherein D represents a group:



wherein n is an integer from 0 to 3, and each of R^5 and R^6 is independently hydrogen, -C_1-C_6 alkyl, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl, halogen, -CN, -CO_2H, -CO_2C_1-C_6 alkyl, -$CONH_2$, -$CONHC_1$-C_6 alkyl, -CONH(C_1-C_6 alkyl)$_2$, -CHO, -CH_2OH, -CF_3, -OC_1-C_6 alkyl, -SC_1-C_6 alkyl, -SOC_1-C_6 alkyl, -SO_2C_1-C_6 alkyl, -NH_2 or -NHCOMe;

or any combination of R^1, R^2, R^3, and R^4 together with the atoms to which they

are attached form a 5 to 8 membered heterocyclic ring;

or any combination of R^1, R^2, R^3, and R^4 together with the carbon atom to which they are attached form a C_3-C_8 cycloalkyl ring;

B represents a) a $-(CH_2)_mA$ group wherein m is an integer from 0 to 1 and the group A represents a 5- or 6-membered heterocyclic ring, which heterocyclic ring may be optionally fused to a benzene ring or to a further 5-, 6- or 7-membered heterocyclic ring containing one or more nitrogen atoms, wherein at least one of the said heterocyclic rings may also contain an oxygen or sulphur atom, and wherein any of the rings may be optionally substituted with one or more substituents selected from hydrogen, halogen, $-C_1$-C_4 perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl, $-CONH_2$, a group -D wherein D is as defined above, $-R^7$, $-OR^7$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-NHR^7$, $-NR^7R^7$, $-CO_2R^7$ or $-CONHR^7$ wherein R^7 is $-C_1$-C_6 alkyl, $-C_2$-C_6 alkenyl, $-C_2$-C_6 alkynyl, $-C_3$-C_8 cycloalkyl or $-C_4$-C_8 cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl, $-C_1$-C_4 perfluoroalkyl, $-C_1$-C_6 alkyl, $-C_2$-C_6 alkenyl, $-C_2$-C_6 alkynyl, $-C_3$-C_8 cycloalkyl, $-C_4$-C_8 cycloalkenyl, $-OC_1$-C_6 alkyl, $-SC_1$-C_6 alkyl, tetrazol-5-yl, a group -D wherein D is as defined above or a heteroaryl or heteroarylmethyl group;

b) a ZR^8 group wherein Z is -C(=O)-, -C(=O)O-, -C(=O)S-, $-CH_2O-$, $-CH_2OC(=O)-$, -C(=S)-, -C(=S)O-, $-CH_2S-$, $-CH_2OC(=O)C(=O)O-$, $-CH_2OSO_2-$, -NHC(=O)O-, $-CH_2OC(=O)NH-$ or $-CH_2C(=O)O-$ group and R^8 is hydrogen, $-C_1$-C_{18} alkyl, $-C_2$-C_{18} alkenyl, $-C_2$-C_{18} alkynyl, $-(C_1$-C_6 alkyl)OC_1-C_6 alkyl, $-(C_1$-C_6 alkyl)SC_1-C_6 alkyl, $-(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl)OC_1-C_6 alkyl, $-C_3$-C_8 cycloalkyl, $-C_4$-C_8 cycloalkenyl, a group D as defined above or a group A as defined above;

c) a $-CH_2NR^9R^{10}$ group or a $-CONR^9R^{10}$ group wherein each of R^9 and R^{10} is independently hydrogen, $-C_1$-C_6 alkyl, $-C_3$-C_8 cycloalkyl, pyridinyl, a group D as defined above or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

Hereafter in this specification the term "compound" includes "salt" or "hydrate"

unless the context requires otherwise.

As used herein the term "halogen" or its abbreviation "halo" means fluoro, chloro, bromo or iodo.

As used herein the term "C_1-C_6 alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to six carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl.

As used herein the term "C_1-C_{18} alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to eighteen carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, decyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, and octadecyl. From one to six carbon atoms may be preferred.

As used herein the term "C_2-C_6 alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_2-C_{18} alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to eighteen carbon atoms and having in addition one or more double bonds, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl, 2-methyl-2-propenyl, geranyl, and farnesyl. From two to six carbon atoms may be preferred.

As used herein, the term "C_1-C_4 perfluoroalkyl" refers to straight chain or branched chain groups having from one to four carbon atoms and substituted by more than one fluorine atom. This term would include for example, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3,3,3-trifluoro-n-propyl, hexafluoro-i-propyl, septafluoro-n-propyl, septafluoro-i-propyl, 4,4,4-trifluoro-n-butyl, nonafluoro-n-butyl, nonafluoro-sec-butyl and nonafluoro-i-butyl.

As used herein the term "OC_1-C_6 alkyl" refers to straight chain or branched chain alkoxy groups having from one to six carbon atoms. Illustrative of such alkoxy

groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy and hexoxy.

As used herein the term "SC_1-C_6 alkyl" refers to straight chain or branched chain alkylthio groups having from one to six carbon atoms. Illustrative of such alkyl groups are methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio and hexylthio.

As used herein, the term "C_3-C_8 cycloalkyl" refers to an alicyclic group having from 3 to 8 carbon atoms. Illustrative of such cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "C_4-C_8 cycloalkenyl" refers to an alicyclic group having from 4 to 8 carbon atoms and having in addition one or more double bonds. Illustrative of such cycloalkenyl groups are cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein, the term "side chain of a naturally occurring amino acid" includes the side chains of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glycine, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α–aminoadipic acid, α–amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α–methylserine, ornithine, pipecolic acid, and thyroxine. The amino acid side chains may be protected; for example the carboxyl groups of aspartic acid, glutamic acid and α–aminoadipic acid may be esterified (for example as a C_1-C_6 alkyl ester), the amino groups of lysine, ornithine, 5-hydroxylysine, 4-hydroxyproline may be converted to amides (for example as a COC_1-C_6 alkyl amide) or carbamates (for example as a $C(=O)OC_1$-C_6 alkyl or $C(=O)OCH_2Ph$ carbamate), the hydroxyl groups of 5-hydroxylysine, 4-hydroxyproline, serine, threonine, tyrosine, 3,4-dihydroxyphenylalanine, homoserine, α–methylserine and thyroxine may be converted to ethers (for example a C_1-C_6 alkyl or a (C_1-C_6 alkyl)phenyl ether) or esters (for example a $C(=O)C_1$-C_6 alkyl ester) and the thiol group of cysteine may be converted to thioethers (for example a C_1-C_6 alkyl thioether) or thioesters (for example a $C(=O)C_1$-C_6 alkyl thioester). The stereochemistry at the carbon atom to which the amino acid side chain is attached may be either D or L.

As used herein, the term "5- or 6-membered heterocyclic ring" refers to such rings having from 5 to 6 atoms in the ring wherein the heteroatom(s) may be

one or more nitrogen, oxygen or sulphur atoms. For example heterocycles containing nitrogen, oxygen, or sulphur alone or containing two nitrogen atoms, a nitrogen and an oxygen atom, a nitrogen and a sulphur atom, two nitrogen atoms and an oxygen atom, two nitrogen atoms and a sulphur atom, three nitrogen atoms or four nitrogen atoms.

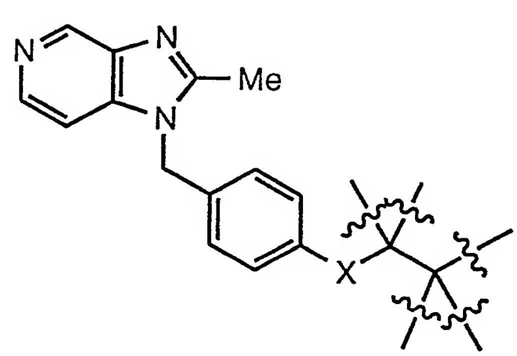
As used herein, the term "nitrogen-containing heterocyclic ring" refers to an aromatic or alicyclic ring comprising one or more nitrogen atoms and optionally one or more other heteroatoms. Illustrative of such rings are pyrrolidine, piperidine, hexamethyleneimine, heptamethylenimine, morpholine and piperazine.

In compounds of this invention, the presence of several asymmetric carbon atoms gives rise to diastereoisomers, each of which consists of two enantiomers, with the appropriate R or S stereochemistry at each chiral center. The invention is understood to include all such diastereoisomers, their optically active enantiomers and mixtures thereof.

The term "pharmaceutically or veterinarily acceptable acid addition salt" refers to a salt prepared by contacting a compound of formula (I) with an acid whose anion is generally considered suitable for human or animal consumption.

Examples of pharmaceutically and/or veterinarily acceptable acid addition salts include the hydrochloride, sulphate, phosphate, acetate, propionate, lactate, maleate, succinate and tartrate salts.

It is considered that the main structural feature of compounds of general formula I that is particularly significant in providing their PAF antagonist activity, is the subunit (i);



(i)

There may be considerable variation of the substituent groups R1, R2, R3, R4

and B without loss of such activity. Any of the the wide range of substituents R^1, R^2, R^3, R^4 and B defined above may be used with retention of PAF antagonist activity. However, the preferred substituent for the group R^3 is the side chain of the amino acid L-leucine (i.e. sec-butyl) and for the group R^4 is a hydrogen atom.

The 1H-2-methylimidazo[4,5-c]pyridinyl group of the subunit is an important requirement for PAF antagonist activity. However, it is expected that PAF antagonist activity may be found in compounds analogous to those of general formula I above, wherein the 1H-2-methylimidazo[4,5-c]pyridinyl group is replaced by a different sp^2 nitrogen heterocycle. The variety of sp^2 nitrogen heterocycles that could provide PAF antagonist activity include those disclosed in our patent application WO 91/17157 and those recently described by Whittaker (Whittaker, M., Curr. Opin. Thera. Patents 2(5), 583-623 (1992)) and Cooper (Cooper, K., *et al.*, J. Med. Chem. 35(17), 3115-3129 (1992)). The exact nature of the interaction of the sp^2 nitrogen heterocycle and the receptor has not been determined, but it would appear that it is important for the heterocycle to possess at least one unsubstituted sp^2 nitrogen atom within the heterocyclic ring.

Although in this application the only substituents claimed for the subunit (i) are R^1, R^2, R^3, R^4 and B it is understood that the introduction of further substituents on the 2-methylimidazo[4,5-c]pyridinyl group, the benzylic carbon atom and/or the 1,4-disubstituted phenyl ring of subunit (i) will lead to compounds that retain PAF antagonist activity.

Preferred compounds include those in which, independently or in any compatible combination;

X represents a -C(=O)- group or a -S(=O)$_2$- group;

R^1 represents a hydrogen atom, a -C_1-C_6 alkyl (for example methyl or ethyl) group, a -C_2-C_6 alkenyl (for example allyl) group or a -(C_1-C_6 alkyl)CO_2C_1-C_6 alkyl (for example ethoxycarbonylmethyl) group;

R^2 represents a hydrogen atom or a -C_1-C_6 alkyl (for example methyl or ethyl) group;

R^3 represents a side chain of a naturally occurring amino acid (for example the side chain of leucine or isoleucine), a -(C_1-C_6 alkyl)C_3-C_8 cycloalkyl (for

example cyclopropylmethyl or cyclopentyl methyl) group or a group D;

R^4 represents a hydrogen atom;

in the group D, n represents an integer of 1;

R^5 represents a hydrogen atom or a halogen (for example fluorine) atom;

R^6 represents a hydrogen atom;

B represents a $-(CH_2)_mA$ group, a ZR^8 or a $-CONR^9R^{10}$ group;

m represents an integer of 0;

A represents a furanyl (for example furan-2-yl) group, an oxadiazolyl (for example 1,2,4-oxadiazol-5-yl) group, a benzthiazolyl (for example benzothiazol-2-yl) group or a thienyl (for example thien-2-yl) group;

Z represents a -C(=O)O- group, a $-CH_2O-$ group, a $-CH_2OC(=O)-$ group or a $-CH_2OC(=O)NH-$ group;

R^7 represents a $-C_1-C_6$ alkyl (for example ethyl) group;

R^8 represents a $-C_1-C_{18}$ alkyl (for example methyl, ethyl, i-propyl or hexadecyl) group;

R^9 represents a pyridinyl (for example 2-pyridinyl) group;

R^{10} represents a hydrogen atom.

Particularly preferred compounds include:

1. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate,
2. 1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl)propane,
3. 1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl)butane,
4. 1-Ethoxy-2-benzyl-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)pentane,
5. 1-Methyl-1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-

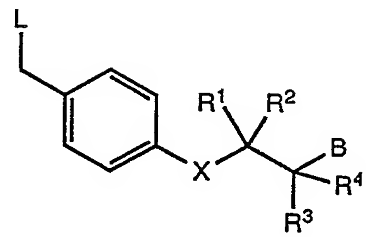
sulphonyl)-2-(2-methylpropyl)-2-(furan-2-yl)-4-methylpentane,

6. 3-Acetoxy-5-methyl-2-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)hexane,
7. 3-Ethylcarbamoyl-5-methyl-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)hexane,
8. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylcarbonyl)-2-(2-methylpropyl)butanoate,
9. 1-(4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)-2-(3-ethyl-1,2,4-oxadiazol-5-yl)-4-methylpentane,
10. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-4-benzthiazol-2-yl-5-methylhexanoate,
11. 1-Heptadecanoyl-2-(2-cyclopentylmethyl)-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)-3-methylbutane,
12. N-2-Pyridinyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl)-2-(1-methylpropyl)propionamide,
13. i-Propyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(cyclopropylmethyl)hex-5-enoate,
14. 1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-thienyl)-3-(4-fluorophenyl)ethane,
15. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)butanoate.

Compounds of general formula I may be prepared by any suitable method known in the art and/or by the following process, which itself forms part of the invention.

According to a second aspect of the invention, there is provided a process for preparing a compound of general formula I as defined above, the process comprising:

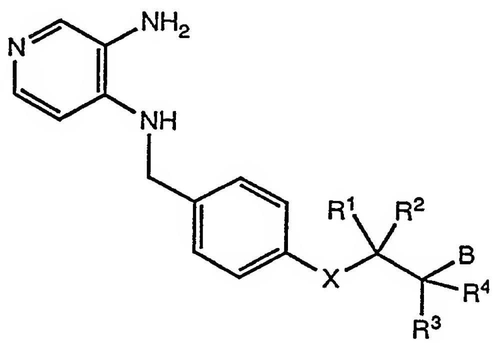
(a) treating 2-methylimidazo[4,5-c]pyridine with a suitable base (e.g. sodium hydride, potassium hydride or sodium bis(trimethylsilyl)amide), followed by a benzyl derivative of general formula II



II

wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy; or

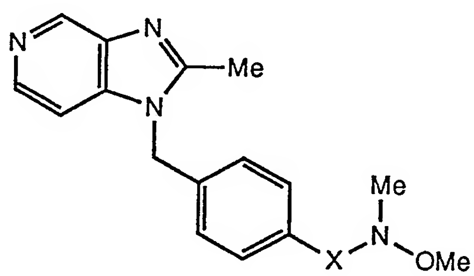
(b) treating a diamino derivative represented by general formula III



III

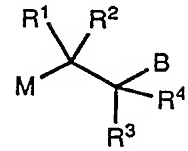
wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, with acetic acid or a suitable derivative thereof; or

(c) treating an amido or sulphonamido derivative represented by general formula IV



IV

wherein X is as defined in general formula I, with a compound of general formula V



V

wherein R^1, R^2, R^3, R^4 and B are as defined in general formula I, and M is MgBr or Li; or

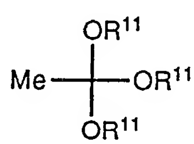
(d) optionally after step (a), step (b) or step (c) converting, in one or a plurality of steps, a compound of general formula I into another compound of general formula I.

The reaction of step (a) can for preference be conducted in an aprotic solvent (e.g. tetrahydrofuran, N,N-dimethylformamide or acetonitrile) to yield compounds of general formula I. The reaction can yield an isomeric mixture, which is separated by chromatography to yield compounds of general formula I.

In step (b), derivatives of acetic acid, which are suitable substrates for the reaction include acetyl halides of general formula VI

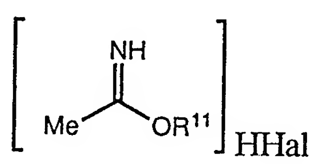
$$MeCO_2Hal \qquad \text{VI}$$

wherein Hal is fluoride, chloride, bromide or iodide; trialkylorthoesters of general formula VII



VII

wherein R^{11} is $-C_1$-C_6 alkyl; imino ether salts of general formula VIII



VIII

wherein R^{11} is $-C_1$-C_6 alkyl and Hal is fluoride, chloride, bromide, or iodide, or acetic anhydride. Acetyl halides of general formula VI, trialkylorthoesters of general formula VII and imino ether salts of general formula VIII are available

in the art or can be prepared by methods analogous to those known in the art

The reaction of step (c) can for preference be conducted in an aprotic solvent (e.g. tetrahydrofuran) to yield compounds of general formula I.

By means of step (d) certain compounds of general formula I may be converted into another compound of general formula I; by

(i) treating a compound of general formula I wherein R^1 represents a hydrogen atom with a base, such as lithium diisopropylamide, in an aprotic solvent (e.g. tetrahydrofuran or diethyl ether) followed by an electrophile of the general formula IX

$$LR^1 \qquad\qquad IX$$

wherein R^1 is $-C_1-C_6$ alkyl, $-C_3-C_6$ alkenyl, $-CO_2C_1-C_6$ alkyl, $-SC_1-C_6$ alkyl, $-(C_1-C_6$ alkyl$)CO_2C_1-C_6$ alkyl, $-(C_1-C_6$ alkyl$)SC_1-C_6$ alkyl, $-(C_1-C_6$ alkyl$)OC_1-C_6$ alkyl and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoro-methanesulphonyloxy. Electrophiles of the general formula IX are available in the art or can be prepared by methods analogous to those known in the art, or:

(ii) by means of step (d) compounds of general formula I wherein B is a $-CO_2NR^9R^{10}$ group wherein R^9 and R^{10} are as defined in general formula I, may be prepared by the following methods;

(a) by treatment of a compound of general formula I wherein B is a $-CO_2R^8$ group wherein R^8 is a benzyl group with hydrogen in the presence of a noble metal catalyst (eg 10% palladium on charcoal) to give a carboxylic acid which is then treated with an amine of general formula HNR^9R^{10} in the presence of a coupling reagent (e.g. 1,3-dicyclohexylcarbodiimide); or

(b) by treatment of a compound of general formula I wherein B is a $-CO_2R^8$ group wherein R^8 is a lower alkyl with a dimethylaluminium amide of general formula X

$$(Me)_2AlNR^9R^{10} \qquad\qquad X$$

wherein R^9 and R^{10} are as defined in general formula I, which is prepared *in situ* from trimethylaluminium and an amine of general formula HNR^9R^{10}; or

(iii) also by means of step (d) certain compounds of general formula I wherein B is a ZR^8 group wherein Z is $-CH_2O-$ and R^8 is hydrogen may be prepared by treatment of a compound of general formula I wherein B is a ZR^8 group wherein Z is -C(=O)O- and R^8 is other than hydrogen with a suitable reducing agent (e.g. lithium aluminium hydride); or

(iv) also by means of step (d) certain compounds of general formula I wherein B is a ZR^8 group wherein Z is $-CH_2O-$ and R^8 is other than hydrogen may be prepared by treatment of a compound of general formula I wherein B is a ZR^8 group wherein Z is $-CH_2O-$ and R^8 is hydrogen with a suitable base in an aprotic solvent followed by an electrophile of general formula XI

$$LR^8 \qquad\qquad XI$$

wherein R^8 is $-C_1-C_{18}$ alkyl, $-C_3-C_{18}$ alkenyl, $-C_3-C_{18}$ alkynyl, $-(C_1-C_6$ alkyl)OC_1-C_6 alkyl, $-(C_1-C_6$ alkyl)SC_1-C_6 alkyl, $-(C_1-C_6$ alkyl)$O(C_1-C_6$ alkyl)OC_1-C_6 alkyl, $-C_3-C_8$ cycloalkyl, $-C_4-C_8$ cycloalkenyl, or a group D wherein n is an integer from 1 to 3 and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy. Electrophiles of the general formula XI are available in the art or can be prepared by methods analogous to those known in the art; or

(v) also by means of step (d) certain compounds of general formula I wherein B is a ZR^8 group wherein Z is $-CH_2OC(=O)-$ and R^8 is other than hydrogen may be prepared by treatment of a compound of general formula I wherein B is a ZR^8 group wherein Z is $-CH_2O-$ and R^8 is hydrogen with a suitable carboxylic acid derivative of general formula XII

$$R^8C(=O)Q \qquad\qquad XII$$

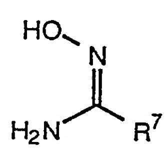
wherein Q is a hydrogen, halide or a $-(O=)CR^8$ group. The conditions for this reaction will depend on the nature of the group Q and will be apparent to one skilled in the art. Carboxylic acids of the general formula XII are available in the art or can be prepared by methods analogous to those known in the art; or

(vi) also by means of step (d) certain compounds of general formula I wherein B is a ZR^8 group wherein Z is $-CH_2OC(=O)NH-$ and R^8 is other than hydrogen may be prepared by treatment of a compound of general formula I wherein B is a ZR^8 group wherein Z is $-CH_2O-$ and R^8 is hydrogen with an isocyanate of general formula XIII

$$R^8\text{-}N{=}C{=}O \qquad \text{XIII}$$

wherein R^8 is as defined in general fromula I. Isocyanates of the general formula XIII are available in the art or can be prepared by methods analogous to those known in the art; or

(vii) also by means of step (d) certain compounds of general formula I wherein B is a 1,2,4-oxadiazol-5-yl group may be prepared by treatment of a compound of general formula I wherein B is a $-CO_2H$ group with pentafluorophenol and a coupling agent such as N-(3-dimethylaminopropyl)-N'-ethylcarodiimide in a solvent such as dichloromethane. The resulting pentafluorophenyl ester is treated with an amide oxime of general formula XIV



XIV

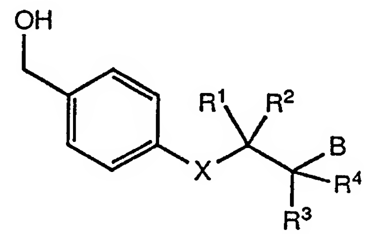
wherein R^7 is as defined in general formula I in a suitable aprotic solvent (e.g. chloroform), followed by cyclisation under Dean-Stark conditions in suitable solvent (e.g. xylene, toluene, benzene or ethyl acetate). The cyclisation may be aided by the addition of activated molecular sieves. Amide oximes of general formula XIV are known in the art or may be prepared by methods analogous to those known in the art; or

(viii) also by means of step (d) certain compounds of general formula I wherein X is a sulphone group may be prepared by treating a compound of general formula I, wherein R^1, R^2, R^3, R^4 and B are as defined in general formula I and X represents -S-, with a suitable oxidising agent (for example metachloroperbenxoic acid); or

(ix) also by means of step (d) certain compounds of general formula I wherein X is a thiocarbonyl group may be prepared by treating a compound of general

formula I, wherein R^1, R^2, R^3, R^4 and B are as defined in general formula I and X represents a -(C=O)- group, with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide.

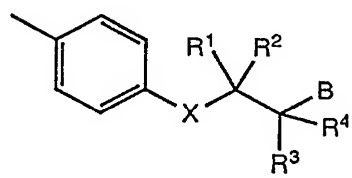
Benzyl derivatives of general formula II may be prepared by treatment of a compound of general formula XV



XV

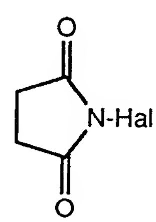
wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, with thionylchloride.

In a second method, benzyl derivatives of general formula II wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, may also be prepared by treatment of a compound of general formula XVI



XVI

wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, with a compound of general formula XVII

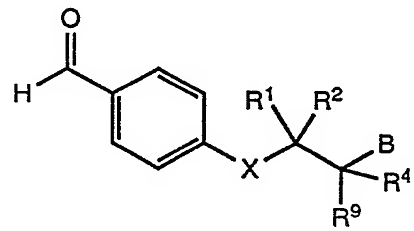


XVII

wherein Hal is fluoride, chloride, bromide or iodide, in the presence of a suitable radical initiator (e.g. 2,2'-azobis(2-methylpropionitrile)) in a suitable solvent (e.g. benzene or carbon tetrachloride). Compounds of general formula XVII are

available in the art.

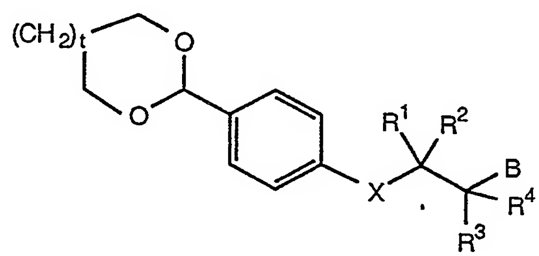
Compounds of general formula XV wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, may be prepared by the reduction of a compound of general formula XVIII



XVIII

wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, with a reducing agent such as lithium aluminium hydride

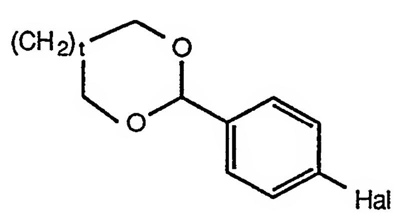
Compounds of general formula XVIII may be prepared by treating an acetal derivative represented by general formula XIX



XIX

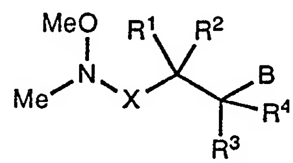
wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I and t is an integer of 0 or 1, with a suitable acid (for example hydrochloric acid), in a suitable solvent, such as acetone.

Compounds of general formula XIX may be prepared by treating a haloarenyl derivative represented by general formula XX



XX

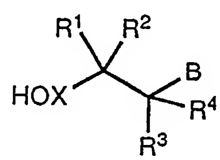
wherein Hal is fluoride, chloride, bromide or iodide, with a suitable metallating agent (for example t-butyl lithium), followed by a compound of general formula XXI



XXI

wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I. Compounds of general formula XX are acetals of commercially available p-halobenzaldehydes.

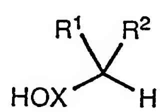
Compounds of general formula XXI may be prepared by treating a carboxylic or sulphonic acid derivative represented by general formula XXII



XXII

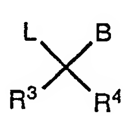
wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, with a suitable activating agent (e.g. thionyl chloride), followed by a N,O-dimethylhydroxylamine hydrochloride in the presence of suitable base such as triethylamine.

Compounds of general formula XXII may be prepared by treating a carboxylic or sulphonic acid derivative represented by general formula XXIII



XXIII

wherein R^1, R^2 and X are as defined in general formula I, with a strong base (e.g. n-butyllithium), followed by a compound of general formula XXIV

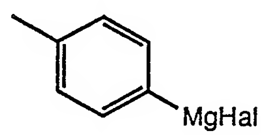


XXIV

wherein R^3, R^4 and B are as defined in general formula I. Compounds of

general formulae XXIII and XXIV are available in the art or may be prepared by methods known to those skilled in the art.

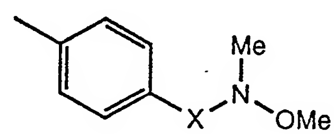
Compounds of general formula XVI may be prepared by treating a Grignard reagent represented by general formula XXV



XXV

wherein Hal is fluoride, chloride, bromide or iodide with a compound of general formula XXI wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I. Compounds of general formula XXV may be prepared from p-halotoluene and magnesium.

In a second method, compounds of general formula XVI may be prepared by treating a sulphonamide or carboxamide derivative of general formula XXVI



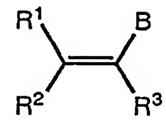
XXVI

wherein X is as defined in general formula I, with a suitable metallo derivative of general formula V, wherein R^1, R^2, R^3, R^4 and B are as defined in general formula I, and M is MgBr or Li, in an aprotic solvent (e.g. tetrahydrofuran).

Compounds of general formula XVI wherein X is a sulphone group may be prepared by treating an aryl thio derivative represented by general formula XVI, wherein R^1, R^2, R^3, R^4 and B are as defined in general formula I and X represents -S-, with a suitable oxidising agent (for example metachloroperbenxoic acid).

(Compounds of general formula XVI wherein X is a thiocarbonyl group may be prepared by treating a carbonyl compound of general formula XVI, wherein R^1, R^2, R^3, R^4 and B are as defined in general formula I and X represents a -(C=O)- group, with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide.

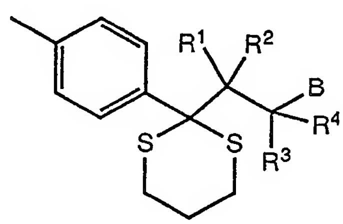
Compounds of general formula XVI, wherein R^1, R^2, R^3, R^4 are as defined in general formula I, X represents -S- and B represents a $-CO_2R^8$ group wherein R^8 is as defined in general formula I but is other than hydrogen, may be prepared by treating 4-methylthiophenol with a suitable base (e.g. sodium hydride), followed by a α,β-unsuturated compound of general formula XXVII



XXVII

wherein R^1, R^2, R^3 and B are as defined in general formula I and B represents a $-CO_2R^8$ group wherein R^8 is as defined in general formula I but is other than hydrogen, in a suitable aprotic solvent (e.g. tetrahydrofuran). Compounds of general formula XXVII are available in the art.

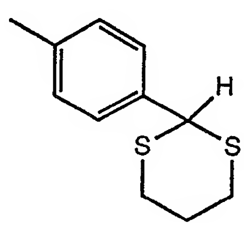
Compounds of general formula XVI wherein X represents a carbonyl group may be prepared by treating a dithiane derivative represented by general formula XXVIII



XXVIII

wherein R^1, R^2, R^3, R^4 and B are as defined in general formula I, with a suitable oxidant (e.g. mercury(II)).

Compounds of general formula XXVIII, wherein B represents a $-CO_2R^8$ group wherein R^8 is as defined in general formula I but is other than hydrogen, may be prepared by treating a dithiane derivative represented by formula XXIX



XXIX

with a suitable base (for example n-butyl lithium), followed by a compound of

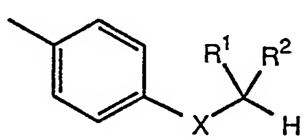
general formula XXVII wherein B represents a $-CO_2R^8$ group wherein R^8 is as defined in general formula I but is other than hydrogen. Compounds of formula XXIX is available in the art.

Compounds of general formula XVI wherein R^1 is a hydrogen atom and B is a $-CO_2H$ group may be prepared by the decarboxylation of a compound of general formula XVI, wherein R^2, R^3 and R^4 are as defined in general formula I, R^1 is a $-CO_2H$ group and B is a $-CO_2H$ group by heating in the presence of an acid or base catalyst.

Compounds of general formula XVI wherein R^1 is a hydrogen atom and B is a $-CO_2C_1-C_{18}$ alkyl group may be prepared by the esterification of a compound of general formula XVI, wherein R^2, R^3 and R^4 are as defined in general formula I, R^1 is a hydrogen atom and B is a $-CO_2H$ group with the appropriate alcohol. The reaction may be catalysed by an acid catalysed or may be conducted by formation of an intermediate activated ester.

Compounds of general formula XVI wherein R^1 is a $-CO_2H$ group and B is a $-CO_2H$ group may be prepared by the acid or base catalysed hydrolysis of a compound of general formula XVI, wherein R^2, R^3 and R^4 are as defined in general formula I, R^1 is a $-CO_2C_1-C_6$ alkyl group and B is a $-CO_2C_1-C_6$ alkyl group.

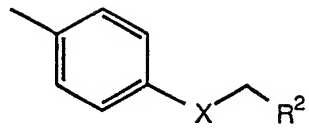
In another method, compounds of general formula XV may be prepared by treating a compound represented by general formula XXX



XXX

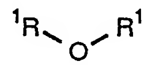
wherein R^1 is a $-CO_2C_1-C_6$ alkyl group and R^2 and X are as defined in general formula I with a suitable base (e.g. potassium t-butoxide) in an aprotic solvent (e.g. N,N-dimethylformamide) followed by a compound of general formula XXIV.

Compounds of general formula XXX may be prepared by treating a compound of general formula XXXI



XXXI

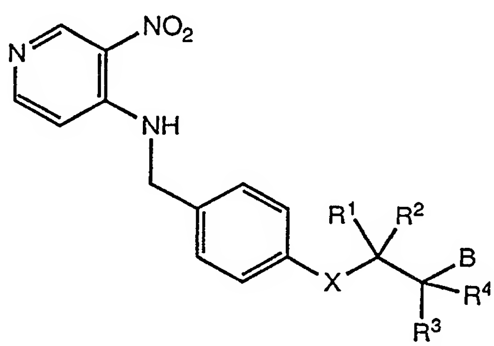
wherein X and R^2 is as defined in general formula I with a suitable base (e.g. lithium diisopropyl amide) in an aprotic solvent (e.g. tetrahydrofuran) followed by a compound of general forumla XXXII



XXXII

wherein R^1 is a $-CO_2C_1-C_6$ alkyl group. Compounds of general formula XXXI and of general formula XXXII are available in the art or may be prepared by methods known to those skilled in the art.

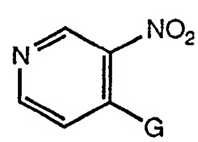
Compounds of general formula III may be prepared by treating a nitro derivative represented by general formula XXXIII



XXXIII

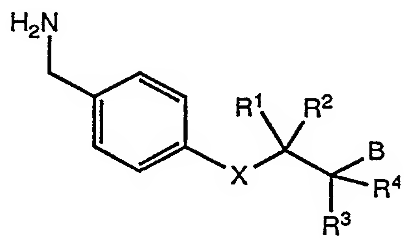
wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, with a suitable reducing agent (for example hydrogen), in the presence of a catalyst such as palladium or platinum.

Substituted 1,2-nitroamines of general formula XXXIII may be prepared by a number of methods. The first of these methods involves the treatment of a nitro compound of general formula XXXIV



XXXIV

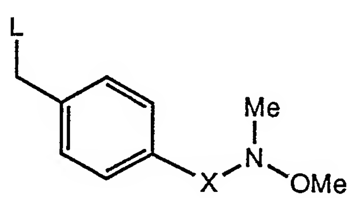
wherein G is halo or C_1-C_6 alkoxy; is treated with an amino compound of general formula XXXV



XXXV

wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I. Nitro compounds of general formula XXXIV are available in the art or can be prepared by methods analogous to those known in the art. Amino compounds of general formula XXXV can be prepared by treatment of a compound of general formula II with hexamethylenetetramine followed by treatment with ethanolic hydrochloric acid or by sequential treatment of a compound of general formula II with sodium azide followed by triphenylphosphine in 'wet' tetrahydrofuran or by hydrogenation over a suitable catalyst.

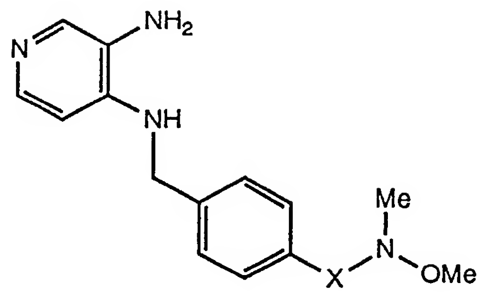
Compounds of general formula IV may be prepared by treating 2-methylimidazo[4,5-c]pyridine with a suitable base (e.g. sodium hydride, potassium hydride or sodium bis(trimethylsilyl)amide), followed by a compound of general formula XXXVI



XXXVI

wherein X is as defined in general formula I and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy.

In a second procedure, compounds of general formula IV may be prepared by treatment of a diamino derivative represented by general formula XXXVII



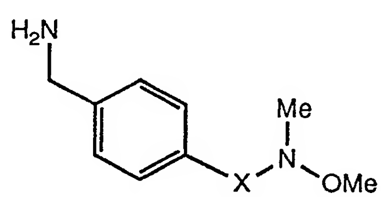
XXXVII

wherein X is as defined in general formula I, with acetic acid, acetic anhydride, an acetyl halide of general formula VI, a trialkylorthoester of general formula VII or an imino ether salt of general formula VIII acid.

Compounds of general formula XXXVI may be prepared by treating an amide or sulphonamide derivative represented by general formula XXVI, wherein X is as defined in general formula I, with a suitable halogenating agent, for example a compound of general formula XVII wherein Hal is fluoride, chloride, bromide or iodide in the presence of a suitable radical initiator (e.g. 2,2'-azobis(2-methylpropionitrile)) in a suitable solvent (e.g. benzene or carbon tetrachloride).

Compounds of general formula XXVI may be prepared by treating p-toluenecarbonyl chloride or p-toluenesulphonyl chloride with N,O-dimethylhydroxylamine in the presence of a suitable base (e.g. triethylamine).

Compounds of general formula XXXVII may be prepared by treating a nitro derivative represented by general formula XXXIV with a compound of general formula XXXVIII



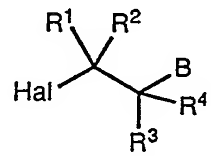
XXXVIII

wherein X is as defined in general formula I.

Amino compounds of general formula XXXVIII can be prepared by treatment of a compound of general formula XXXVI with hexamethylenetetramine followed by treatment with ethanolic hydrochloric acid or by sequential treatment of a compound of general formula XXXVI with sodium azide followed by

triphenylphosphine in wet tetrahydrofuran or by hydrogenation over a suitable catalyst.

Compounds of general formula V may be prepared by treating a halo derivative represented by general formula XXXIX



XXXIX

wherein R^1, R^2, R^3, R^4 and B are as defined in general formula I, with a suitable metal (e.g. lithium or magnesium) or with an alkyl lithium. Compounds of general formula XXXIX are available in the art or may be prepared by methods known to those skilled in the art.

The appropriate solvents employed in the above reactions are solvents wherein the reactants are soluble but do not react with the reactants. The preferred solvents vary from reaction to reaction and are readily ascertained by one of ordinary skill in the art.

Compounds of general formulae II, III, and IV are valuable intermediates in the preparation of compounds of general formula I, as are other novel compounds specifically or generically disclosed herein. According to a third aspect of the invention, there is therefore provided a compound of general formula II. According to a fourth aspect of the invention, there is provided a compound of general formula III. According to a fifth aspect of the invention, there is provided a compound of general formula IV.

This invention also relates to a method of treatment for patients (or animals including mammalian animals raised in the dairy, meat, or fur trades or as pets) suffering from disorders or diseases which can be attributed to PAF as previously described, and more specifically, a method of treatment involving the administration of PAF antagonists of general formula I as the active ingredient. In addition to the treatment of warm blooded animals such as mice, rats, horses, cattle, pigs, sheep, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

According to a sixth aspect of the invention there is provided a compound of

general formula I for use in human or veterinary medicine particularly in the management of diseases mediated by PAF; compounds of general formula I can be used among other things to reduce inflammation and pain, to correct respiratory, cardiovascular, and intravascular alterations or disorders, and to regulate the activation or coagulation of platelets, to correct hypotension during shock, the pathogenesis of immune complex deposition and smooth muscle contractions.

According to an seventh aspect of the invention there is provided the use of a compound of general formula I in the preparation of an agent for the treatment or prophylaxis of PAF-mediated diseases, and/or the treatment of inflammatory disorders; such as rheumatoid arthritis, osteoarthritis and eye inflammation, cardiovascular disorder, thrombocytopenia, asthma, endotoxin shock, adult respiratory distress syndrome, glomerulonephritis, immune regulation, gastric ulceration, transplant rejection, psoriasis, allergic dermatitis, urticaria, multiple sclerosis, cerebral, myocardial and renal ischemia and any other condition in which PAF is implicated.

Compounds of general formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

According to an eighth aspect of the invention there is provided a pharmaceutical or veterinary formulation comprising a compound of general formula I and a pharmaceutically and/or veterinarily acceptable carrier. One or more compounds of general formula I may be present in association with one or more non-toxic pharmaceutically and/or veterinarily acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients.

The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method

known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occuring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose

any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical application to the skin compounds of general formula I may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

For topical applications to the eye, compounds of general formula I may be made up into a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers, preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorohexidine, and thickening agents such as hypromellose may also be included.

Compounds of general formula I may be administered parenterally in a sterile medium. The drug depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

Compounds of general formula I may be used for the treatment of the respiratory tract by nasal or buccal administration of, for example, aerosols or sprays which can disperse the pharmacological active ingredient in the form of a powder or in the form of drops of a solution or suspension. Pharmaceutical compositions with powder-dispersing properties usually contain, in addition to the active ingredient, a liquid propellant with a boiling point below room temperature and, if desired, adjuncts, such as liquid or solid non-ionic or anionic surfactants and/or diluents. Pharmaceutical compositions in which the pharmacological active ingredient is in solution contain, in addition to this, a suitable propellant, and furthermore, if necessary, an additional solvent and/or a stabiliser. Instead of the propellant,

compressed air can also be used, it being possible for this to be produced as required by means of a suitable compression and expansion device.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 1.0 mg to about 3.5 g per patient per day). The dosage employed for the topical administration will, of course, depend on the size of the area being treated. For the eyes each dose will be typically in the range from 10 to 100 mg of the drug.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

It is found that the compounds of general formula I exhibit *in vitro* antagonistic activities with respect to PAF. Compounds of general formula I inhibit PAF-induced functions in both the cellular and tissue levels by changing the PAF binding to its specific receptor site. The ability of compounds of general formula I to inhibit the binding of PAF to its specific receptor binding site on human platelet plasma membranes is measured according to Example 16.

The following examples illustrate the invention, but are not intended to limit the scope in any way.

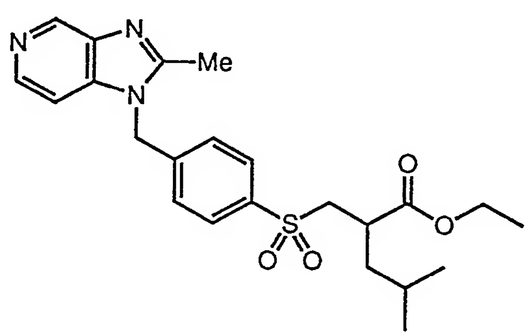
The following abbreviations are used in the Examples:-

DCM - Dichloromethane
DMF - Dimethylformamide
NBS - N-Bromosuccinimide
THF - Tetrahydrofuran

Column chromatography was performed with "flash" grade silica gel. Unless otherwise stated anhydrous magnesium sulphate or anhydrous sodium sulphate was used for drying organic solutions. Unless otherwise stated ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer at 250 MHz and 62.9 MHz respectively using $CDCl_3$ as a solvent and internal reference and are reported as δ ppm from TMS.

Example 1

Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate



(a) t-Butyl 2-(4-methylphenylsulphonyl)ethanoate

n-Butyllithium (1.6 M in hexane; 34.8 ml, 55.6 mmol) was added to a stirred solution of methyl 4-methylphenylsulphone (8.7 g, 50.5 mmol) in dry THF (250 ml) at -78°C. The reaction mixture turned a yellow colour and after stirring for 0.5 h at -78°C a solution of di-t-butyl dicarbonate (5.5 g, 25.3 mmol) in dry THF (15 ml) was added. The mixture was stirred at -78°C for 1 h, allowed to warm to room temperature and stirred for 3 h. Ethyl acetate and aqueous ammonium chloride were added. The organic layer was separated, dried, filtered and evaporated. Chromatography (20-60% ethyl acetate in hexane) gave t-butyl 2-(4-methylphenylsulphonyl)ethanoate (6.17 g, 90%) as a colourless oil.

δ_H (400 MHz) 7.82 (2H, d), 7.36 (2H, d), 4.00 (2H, s), 2.45 (3H, s), 1.39 (9H, s).

(b) t-Butyl 2-(4-methylphenylsulphonyl)-3-(t-butoxycarbonyl)-5-methylhexanoate

Potassium t-butoxide (3.11 g, 27.4 mmol) was added to a stirred solution of t-butyl 2-(4-methylphenylsulphonyl)ethanoate (6.17 g, 22.8 mmol) in dry DMF (100 ml). The mixture was stirred at room temperature for 10 min and t-butyl 2-bromo-4-methylpentanoic acid (6.88 g, 27.4 mmol) added. The mixture was stirred at room temperature for 48 h and ethyl acetate and aqueous ammonium chloride added. The organic layer was separated, washed with water, dried, filtered and evaporated. Chromatography (0-20% ethyl acetate in hexane) gave t-butyl 2-(4-methylphenylsulphonyl)-3-(t-butoxycarbonyl)-5-methylhexanoate (7.3 g, 72%) as a colourless oil.

δ_H (400 MHz) 7.78 (2H, dd), 7.33 (2H, d), 4.24 (0.5H, d), 4.11 (0.5H, m), 3.14 (0.5H, m), 2.97 (0.5H, m), 2.45 (3H, s), 1.98-1.22 (21H, m), 0.98-0.82 (6H, m).

(c) 2-(4-Methylphenylsulphonyl)-3-(hydroxycarbonyl)-5-methylhexanoic acid

Trifluoroacetic acid (31.2 ml, 406 mmol) was added dropwise to a stirred solution of t-butyl 2-(4-methylphenylsulphonyl)-3-(t-butoxycarbonyl)-5-methylhexanoate (7.3 g, 16.5 mmol) in DCM (18 ml). The mixture was stirred at room temperature for 3 h, and DCM and brine were added. The organic layer was separated, dried, filtered and evaporated to give 2-(4-methylphenylsulphonyl)-3-(hydroxycarbonyl)-5-methylhexanoic acid (4.27 g, 78%) as a pale brown oil.

δ_H (400 MHz) 7.78 (2H, dd), 7.37 (2H, d), 4.56 (0.6H, d), 4.30 (0.4H, m), 3.39-3.15 (1H, m), 2.46 (3H, s), 1.90-1.55 (3H, m), 1.00-0.87 (6H, m).

(d) 3-(4-Methylphenylsulphonyl)-2-(2-methylpropyl)propanoic acid

A mixture of 2-(4-methylphenylsulphonyl)-3-(hydroxycarbonyl)-5-methylhexanoic acid (4.27 g, 13.0 mmol) and sodium hydrogen carbonate (10.92 g, 130 mmol) in DMF (20 ml) was heated at 100°C for 10 h. The mixture was allowed to stand at room temperature for 8 h and ethyl acetate and 2N hydrochloric acid added. The organic layer was separated, washed with water, dried, filtered and concentrated. Chromatography (1% methanol in DCM) gave 3-(4-methylphenylsulphonyl)-2-(2-methylpropyl)propanoic acid (1.24 g, 34%) as a colourless oil.

δ_H (400 MHz) 8.01 (1H, s), 7.80 (2H, dd), 7.35 (2H, d), 3.82 (1H, dd), 3.07 (1H, dd), 2.99-2.90 (1H, m), 2.44 (3H, s), 1.67-1.53 (2H, m), 1.43-1.34 (1H, m), 0.89 (3H, d), 0.82 (3H, d).

(e) Ethyl 3-(4-methylphenylsulphonyl)-2-(2-methylpropyl)propanoate

A solution of 3-(4-methylphenylsulphonyl)-2-(2-methylpropyl)propanoic acid (1.2 g, 4.48 mmol), p-toluene sulphonic acid (4 mg) in ethanol (3.5 ml) and toluene (20 ml) was heated at reflux overnight in a Dean-Stark apparatus. The reaction was cooled and ethyl acetate and brine added. The organic layer was separated, dried and evaporated. Chromatography (10-20% ethyl acetate in hexane followed by 5% methanol in DCM) gave ethyl 3-(4-methylphenylsulphonyl)-2-(2-methylpropyl)propanoate (415 mg, 30%) as a colourless oil.

δ_H 7.80 (2H, dd), 7.36 (2H, d), 4.00-3.97 (2H, m), 3.64 (1H, dd), 3.06 (1H, dd), 3.00-2.89 (1H, m), 2.46 (3H, s), 1.65-1.45 (2H, m), 1.44-1.30 (1H, m), 1.24 (3H, t), 0.92 (3H, d), 0.86 (3H, d).

(f) Ethyl 3-(4-bromomethylphenylsulphonyl)-2-(2-methylpropyl)propanoate

To a solution of ethyl 3-(4-methylphenylsulphonyl)-2-(2-methylpropyl)-propanoate (415 mg, 1.32 mmol) in carbon tetrachloride (20 ml) and NBS (238 mg, 1.32 mmol) heated at reflux was added 2,2'-azobis(isobutylnitrile) (10 mg). The mixture was heated at reflux overnight and allowed to cool to room temperature. DCM and water were added and the organic layer separated, dried, filtered and evaporated. Chromatography (10% ethyl acetate in hexane) gave ethyl 3-(4-bromomethylphenylsulphonyl)-2-(2-methylpropyl)propanoate (209 mg, 53%) as an amorphous solid.

δ_H 7.80 (2H, dd), 7.40 (2H, d), 4.52 (2H, s), 4.08-3.97 (2H, m), 3.70 (1H, dd), 3.08 (1H, dd), 3.03-2.90 (1H, m), 1.65-1.30 (3H, m), 1.26 (3H, t), 0.95 (3H, d), 0.87 (3H, d).

(g) Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate

Sodium hydride (60% dispersion in oil) (20 mg, 0.51 mmol) was added to a stirred solution of 2-methylimidazo[4,5-c]pyridine (64 mg, 0.48 mmol) in a

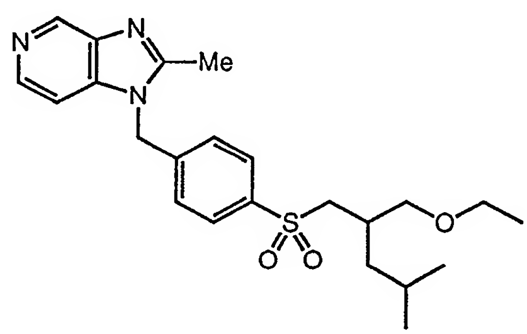
mixture of dry THF (10 ml) and dry DMF (10 ml) under argon at room temperature. After 1 h a solution of ethyl 3-(4-bromomethylphenylsulphonyl)-2-(2-methylpropyl)-propanoate (186 mg, 0.48 mmol) in dry THF (2 ml) was added. The mixture was stirred for 8 h and the solvent was removed under reduced pressure, saturated ammonium chloride was added and the product was extracted with ethyl acetate. The combined organic layers were washed with water, dried, filtered and the solvent was removed. Chromatography (8% methanol in DCM) gave three regioisomers, ethyl 3-(4-(3H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)-2-(2-methylpropyl)propanoate which elutes first, ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methyl-propyl)propanoate which elutes second and ethyl 3-(4-(5H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate which elutes last. The desired regioisomer, ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl)-2-(2-methylpropyl)propanoate (7 mg, 3%), was obtaioned as a colourless oil.

δ_H 9.03 (1H, s), 8.37 (1H, d), 7.78 (2H, dd), 7.35-7.11 (3H, m), 5.39 (2H, s), 4.05-3.95 (2H, m), 3.65 (1H, dd), 3.05 (1H, dd), 3.00-2.88 (1H, m), 1.70-1.30 (3H, m), 1.20 (3H, t), 0.97 (3H, d), 0.90 (3H, d).

Although not claimed in this patent application the other two regioisomers are antagonists of platelet activating factor.

Example 2

1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)propane



(a) N,O-Dimethyl-N-4-methylphenylsulphonyl hydroxylamine

To a solution of triethylamine (26.6 ml, 0.192 mol) in dry THF (200 ml) is added powdered N,O-dimethylhydroxylamine hydrochloride (9.36 g, 0.096 mol) in one portion. The mixture is stirred at room temperature for 0.5 h and powdered 4-methylphenylsulphonyl chloride (18.3 g, 0.096 mol) is added in one portion. The mixture is stirred overnight at room temperature. Saturated ammonium chloride (100 ml) is added and the mixture is extracted with ethyl acetate (3 x 100 ml), the organics are dried, filtered and evaporated. The resulting oil is chromatographed (ethyl acetate in hexane) to give N,O-dimethyl-N-4-methylphenylsulphonyl hydroxylamine the structure of which is confirmed by ^1H n.m.r. spectroscopy.

(b) 1-Ethoxy-2-(2-methylpropyl)-3-(4-methylphenylsulphonyl)propane

A solution of N,O-dimethyl-N-4-methylphenylsulphonyl hydroxylamine (17.2 g, 0.08 mol) in dry THF (50 ml) is added dropwise to a stirred solution of 1-lithio-2-(2-methylpropyl)-3-ethoxypropane (prepared from lithium (0.70 g, 0.1 mol) and 1-bromo-2-(2-methylpropyl)-3-ethoxypropane (22.2 g, 0.1 mol) with sonication) in dry THF (150 ml) at 0°C under argon. The mixture is allowed to slowly warm up to room temperature and is stirred overnight. Saturated ammonium chloride (100 ml) is added and the product is extracted with ethyl acetate (3 x 100 ml). The combined organic layers are washed with water (2 x 100 ml), are dried, filtered and the solvent is removed. Chromatography (ethyl acetate in hexane) gives 1-ethoxy-2-(2-methylpropyl)-3-(4-methylphenylsulphonyl)propane the structure of which is confirmed by ^1H n.m.r. spectroscopy.

(c) 1-Ethoxy-2-(2-methylpropyl)-3-(4-bromomethylphenylsulphonyl)propane

To a solution of 1-ethoxy-2-(2-methylpropyl)-3-(4-methylphenylsulphonyl)-propane (14.9 g, 0.05 mol) in benzene (50 ml) and NBS (8.9 g, 0.05 mol) heated at reflux is added 2,2'-azobis(2-methylpropionitrile) (50 mg). The mixture is heated at reflux for 12 h and is allowed to cool to room temperature. The white precipitate of succinimide that forms is separated and discarded. The filtrate is taken up in DCM (100 ml) and is washed with water (3 x 50 ml) followed by brine (50 ml) and is dried. Filtration, concentration and subsequent chromatography (ethyl acetate in hexane) gives 1-ethoxy-2-(2-methylpropyl)-3-(4-bromomethylphenylsulphonyl)propane the structure of which is confirmed by

^1H n.m.r. spectroscopy.

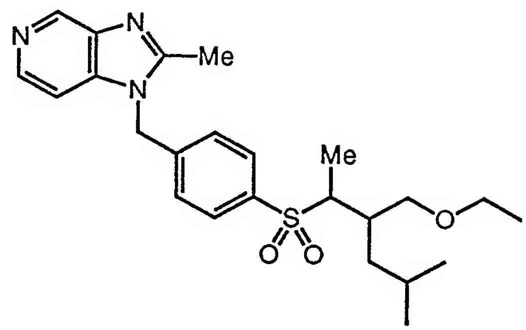
(d) 1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl)propane

Sodium hydride (60% dispersion in oil) (204 mg, 5.1 mmol) is added to a stirred solution of 2-methylimidazo[4,5-c]pyridine (640 mg, 4.8 mmol) in a mixture of dry THF (40 ml) and dry DMF (10 ml) under argon at room temperature. After 1 h a solution of 1-ethoxy-2-(2-methylpropyl)-3-(4-bromomethyl-phenyl-sulphonyl)propane (1.80 g, 4.8 mmol) in dry THF (15 ml) is added. The mixture is stirred for 8 h and the solvent is removed under reduced pressure, saturated ammonium chloride (60 ml) is added and the product is extracted with ethyl acetate (3 x 60 ml). The combined organic layers are washed with water (2 x 50 ml), dried, filtered and the solvent is removed. Chromatography (8% methanol in DCM) gives three regioisomers, 1-ethoxy-2-(2-methylpropyl)-3-(4-(3H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)propane which elutes first, 1-ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)propane which elutes second and 1-ethoxy-2-(2-methylpropyl)-3-(4-(5H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl)propane which elutes last. The structure of the desired regioisomer 1-ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)propane is confirmed by ^1H n.m.r. spectroscopy. Although not claimed in this patent application the other two regioisomers 1-ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methyl-imidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl)propane and 1-ethoxy-2-(2-methylpropyl)-3-(4-(5H-2-methylimidazo-[4,5-c]pyridinylmethyl)phenylsulphonyl)propane are antagonists of platelet activating factor.

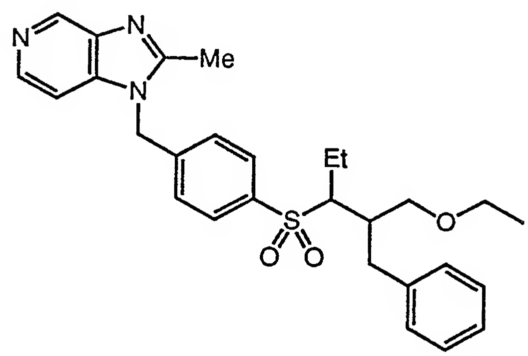
<u>Examples 3-15</u>

The compounds of Examples 3 to 15 are prepared by procedures analogous to the methods of Example 1 and/or Example 2 employing the appropriate starting materials. The structure of each compound is confirmed by ^1H n.m.r. spectroscopy.

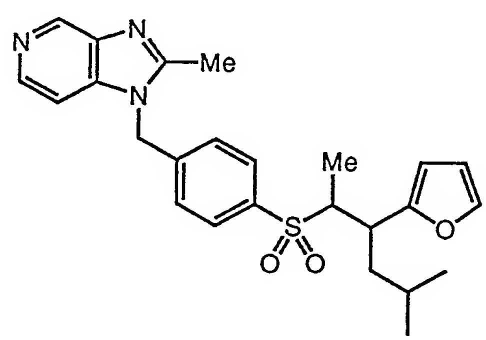
3. 1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl)butane



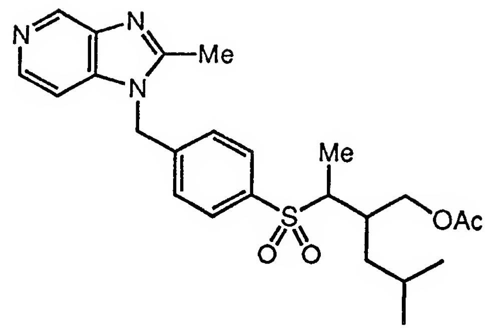
4. 1-Ethoxy-2-benzyl-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)pentane



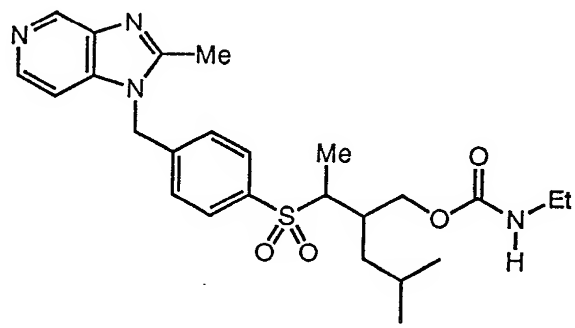
5. 1-Methyl-1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)-2-(furan-2-yl)-4-methylpentane



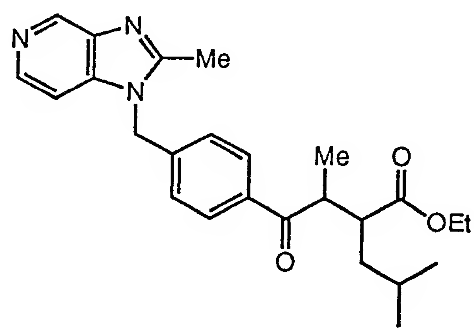
6. 3-Acetoxy-5-methyl-2-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)hexane



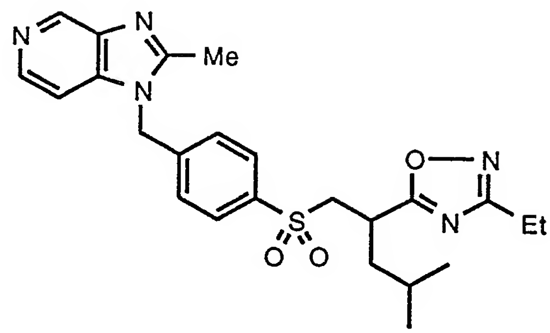
7. 3-Ethylcarbamoyl-5-methyl-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinyl-methyl)phenylsulphonyl)hexane



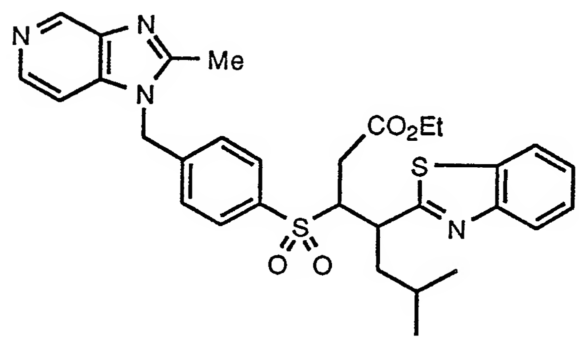
8. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylcarbonyl)-2-(2-methylpropyl)butanoate



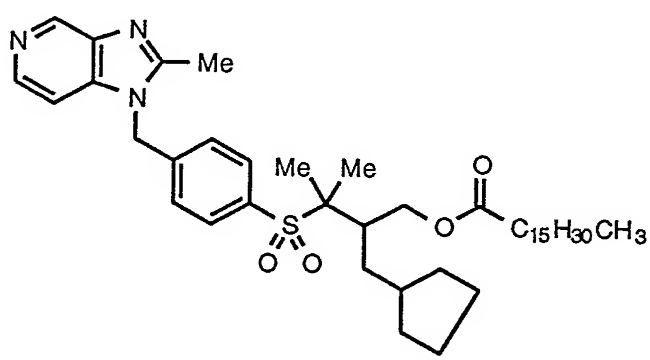
9. 1-(4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)-2-(3-ethyl-1,2,4-oxadiazol-5-yl)-4-methylpentane



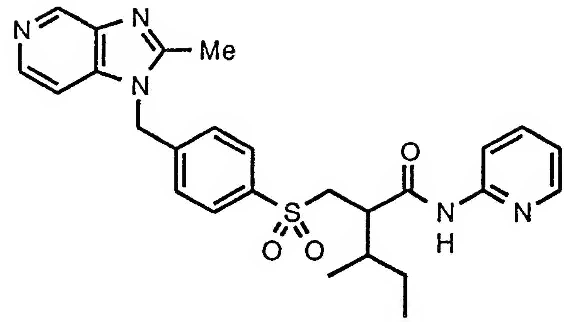
10. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-4-benzthiazol-2-yl-5-methylhexanoate



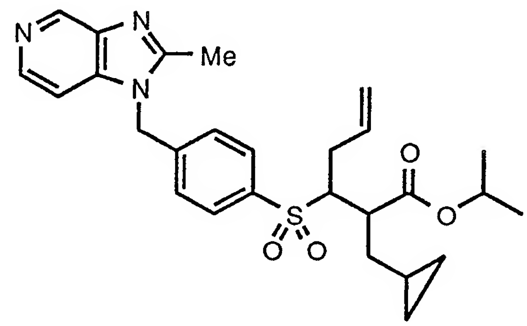
11. 1-Heptadecanoyl-2-(2-cyclopentylmethyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-3-methylbutane



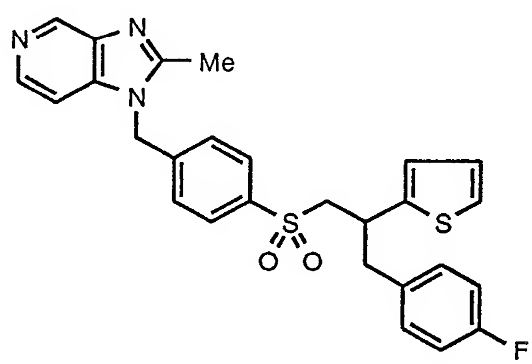
12. N-2-Pyridinyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl)-2-(1-methylpropyl)propionamide



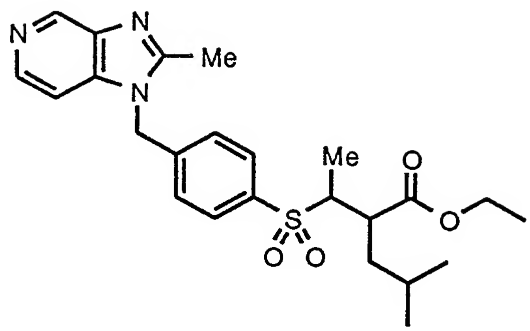
13. i-Propyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl)-2-(cyclopropylmethyl)hex-5-enoate



14. 1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-thienyl)-3-(4-fluorophenyl)ethane



15. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)butanoate



Example 16

Inhibition of [^{3}H]-PAF Receptor Binding

The inhibition of [^{3}H]-PAF binding to human platelet plasma membrane by compounds of general formula I is determined by isotopic labelling and filtration techniques. Platelet concentrates are obtained from a hospital blood bank. These platelet concentrates (500-2500 ml.) are centrifuged at 800 rpm for 10 minutes in a SORVALL RC3B centrifuge to remove the red blood cells present. (The word SORVALL is a trade mark.) The supernatant is subsequently centrifuged at 3,000 rpm in a SORVALL RC3B centrifuge to pellet the platelets present. The platelet rich pellets are resuspended in a minimum volume of buffer (150 mM NaCl, 10 mM Tris, 2 mM EDTA, pH 7.5) and layered onto Ficoll-Paque gradients, 9 ml platelet concentrate to 2 ml Ficoll, and centrifuged at 1,900 rpm for 15 minutes in a SORVALL RT6000 centrifuge. This step removes the residual red blood cells and other nonspecific material such as lymphocytes from the preparation. The platelets which form a band between the plasma and the Ficoll are removed, resuspended in the above buffer and centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge. The pelleted platelets are resuspended in buffer (10 mM Tris, 5 mM $MgCl_2$, 2 mM EDTA, pH 7.0), snap freezed in liquid N_2 and allowed to thaw slowly at room temperature in order to lyse the platelets. The latter step is repeated at least 3 times to ensure proper lysis. The lysed platelets are centrifuged at 3,000 rpm for 10 minutes in a SORVALL RT6000 centrifuge and resuspended in buffer. The latter step is repeated twice in order to remove any cytoplasmic proteins which may hydrolyse the platelet activating factor (PAF) receptor. The prepared platelet membranes may be stored at -70°C. After thawing the prepared membranes are centrifuged in a SORVALL RT6000 at 3,000 rpm for 10 minutes and resuspended in assay buffer.

The assay is conducted by preparing a series of Tris-buffered solutions of the

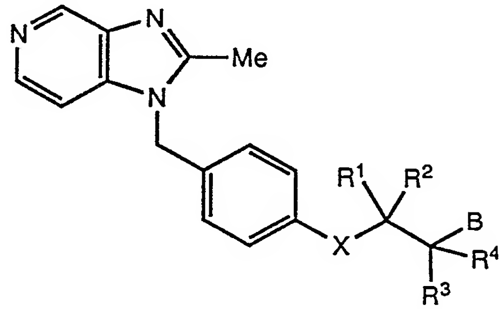
selected antagonist of predetermined concentrations. Each of these solutions contained [^{3}H]-PAF (0.5 nM; 1-*O*-[^{3}H]octadecyl-2-acetyl-*sn*-glycero-3-phosphoryl choline with a specific activity of 132 Ci/mmol), unlabelled PAF (1000 nM), a known amount of the test antagonist, and a sufficient amount of Tris-buffer solution (10 mM Tris, 5 mM $MgCl_2$, pH 7.0, 0.25% BSA) to make the final volume 1 ml. Incubation is initiated by the addition of 100 μg of the isolated membrane fraction to each of the above solutions at 0°C. Two control samples, one (C1) which contained all the ingredients described above except the antagonist and the other (C2) contains C1 plus a 1000-fold excess of unlabelled PAF, are also prepared and incubated simultaneously with the test samples. After 1 hour incubation, each solution is filtered rapidly under vacuo through a WHATMAN GF/C glass fibre filter in order to separate unbound PAF from bound PAF. (The word WHATMAN is a trade mark.) The residue in each case is rapidly washed 4 times with 5 ml cold (4°C) Tris-buffer solution. Each washed residue is dried under vacuum on a sampling manifold and placed into vials containing 20 ml of OPTIPHASE MP scintillation fluid and the radioactivity counted in a liquid scintillation counter. (The word OPTIPHASE is a trade mark.) Defining the counts for total binding with antagonist from a test sample as "TBA"; the counts for total binding from the control sample C1 as "TB"; and the counts for nonspecific binding from the control sample C2 as "NSB", the percent inhibition of each test antagonist can be determined by the following equation:

$$\%\text{Inhibition} = [(TB-TBA)/SB]\times 100$$

where the specific binding SB = TB-NSB

CLAIMS

1. A compound of general formula I;

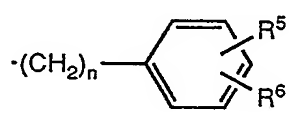


I

wherein:

X represents a -C(=O)-, -C(=S)-, -S(→O)- or $-S(=O)_2-$ group;

R^1, R^2, R^3, and R^4 each independently represents hydrogen, $-C_1-C_6$ alkyl optionally substituted by one or more halogen atoms, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-(C_1-C_6$ alkyl$)CO_2C_1-C_6$ alkyl, $-(C_1-C_6$ alkyl$)SC_1-C_6$ alkyl, $-(C_1-C_6$ alkyl$)OC_1-C_6$ alkyl, $-(C_1-C_6$ alkyl$)N(C_1-C_6$ alkyl$)_2$, $-C_3-C_8$ cycloalkyl, $-C_4-C_8$ cycloalkenyl, $-(C_1-C_6$ alkyl$)C_3-C_8$ cycloalkyl, $-(C_1-C_6$ alkyl$)C_4-C_8$ cycloalkenyl, $-(C_1-C_6$ alkyl$)OC_3-C_8$ cycloalkyl, $-(C_1-C_6$ alkyl$)OC_4-C_8$ cycloalkenyl, $-(C_1-C_6$ alkyl$)SC_3-C_8$ cycloalkyl, $-(C_1-C_6$ alkyl$)SC_4-C_8$ cycloalkenyl, a side chain of a naturally occurring amino acid or a group D wherein D represents a group:



wherein n is an integer from 0 to 3, and each of R^5 and R^6 is independently hydrogen, $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, halogen, -CN, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, $-CONH_2$, $-CONHC_1-C_6$ alkyl, $-CONH(C_1-C_6$ alkyl$)_2$, -CHO, $-CH_2OH$, $-CF_3$, $-OC_1-C_6$ alkyl, $-SC_1-C_6$ alkyl, $-SOC_1-C_6$ alkyl, $-SO_2C_1-C_6$ alkyl, $-NH_2$ or -NHCOMe;

or any combination of R^1, R^2, R^3, and R^4 together with the atoms to which they are attached form a 5 to 8 membered heterocyclic ring;

or any combination of R^1, R^2, R^3, and R^4 together with the carbon atom to which they are attached form a C_3-C_8 cycloalkyl ring;

B represents a) a $-(CH_2)_mA$ group wherein m is an integer from 0 to 1 and the group A represents a 5- or 6-membered heterocyclic ring, which heterocyclic ring may be optionally fused to a benzene ring or to a further 5-, 6- or 7-membered heterocyclic ring containing one or more nitrogen atoms, wherein at least one of the said heterocyclic rings may also contain an oxygen or sulphur atom, and wherein any of the rings may be optionally substituted with one or more substituents selected from hydrogen, halogen, $-C_1-C_4$ perfluoroalkyl, hydroxyl, carbonyl, thiocarbonyl, carboxyl, $-CONH_2$, a group -D wherein D is as defined above, $-R^7$, $-OR^7$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-NHR^7$, $-NR^7R^7$, $-CO_2R^7$ or $-CONHR^7$ wherein R^7 is $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_3-C_8$ cycloalkyl or $-C_4-C_8$ cycloalkenyl each of which is optionally substituted with one or more substituents selected from halogen, hydroxyl, amino, carboxyl, $-C_1-C_4$ perfluoroalkyl, $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_3-C_8$ cycloalkyl, $-C_4-C_8$ cycloalkenyl, $-OC_1-C_6$ alkyl, $-SC_1-C_6$ alkyl, tetrazol-5-yl, a group -D wherein D is as defined above or a heteroaryl or heteroarylmethyl group;

b) a ZR^8 group wherein Z is -C(=O)-, -C(=O)O-, -C(=O)S-, $-CH_2O-$, $-CH_2OC(=O)-$, -C(=S)-, -C(=S)O-, $-CH_2S-$, $-CH_2OC(=O)C(=O)O-$, $-CH_2OSO_2-$, -NHC(=O)O-, $-CH_2OC(=O)NH-$ or $-CH_2C(=O)O-$ group and R^8 is hydrogen, $-C_1-C_{18}$ alkyl, $-C_2-C_{18}$ alkenyl, $-C_2-C_{18}$ alkynyl, $-(C_1-C_6$ alkyl$)OC_1-C_6$ alkyl, $-(C_1-C_6$ alkyl$)SC_1-C_6$ alkyl, $-(C_1-C_6$ alkyl$)O(C_1-C_6$ alkyl$)OC_1-C_6$ alkyl, $-C_3-C_8$ cycloalkyl, $-C_4-C_8$ cycloalkenyl, a group D as defined above or a group A as defined above;

c) a $-CH_2NR^9R^{10}$ group or a $-CONR^9R^{10}$ group wherein each of R^9 and R^{10} is independently hydrogen, $-C_1-C_6$ alkyl, $-C_3-C_8$ cycloalkyl, pyridinyl, a group D as defined above or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 5 to 8 membered nitrogen-containing heterocyclic ring;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

2. A compound as claimed in Claim 1, in which X represents a -C(=O)- group or a $-S(=O)_2-$ group.

3. A compound as claimed in Claims 1 and 2, wherein R^1 represents a hydrogen atom, a $-C_1-C_6$ alkyl (for example methyl or ethyl) group, a $-C_2-C_6$ alkenyl (for

example allyl) group or a $-(C_1-C_6$ alkyl)$CO_2C_1-C_6$ alkyl (for example ethoxycarbonylmethyl) group.

4. A compound as claimed in any one of Claim 1 to 3, wherein R^2 represents a hydrogen atom or a $-C_1-C_6$ alkyl group.

5. A compound as claimed in 1 to 4, wherein R^3 represents a side chain of a naturally occurring amino acid, a $-(C_1-C_6$ alkyl)C_3-C_8 cycloalkyl group or a group D.

6. A compound as claimed in any one of Claims 1 to 5, wherein R^4 represents a hydrogen atom.

7. A compound as claimed in any one of Claims 1 to 6, wherein, in the group D, n represents an integer of 1, R^5 represents a hydrogen atom or a halogen atom and R^6 represents a hydrogen atom.

8. A compound as claimed in any one of Claims 1 to 7, wherein B represents a $-(CH_2)_mA$ group, a ZR^8 or a $-CONR^9R^{10}$ group.

9. A compound as claimed in Claim 8, wherein m represents an integer of 0.

10. A compound as claimed in Claim 8, wherein A represents a furanyl group, an oxadiazolyl group, a benzthiazolyl group or a thienyl group.

11. A compound as claimed in Claim 10, wherein R^7 represents a $-C_1-C_6$ alkyl group.

12. A compound as claimed in Claim 8, wherein Z represents a -C(=O)O- group, a $-CH_2O-$ group, a $-CH_2OC(=O)-$ group or a $-CH_2OC(=O)NH-$ group.

13. A compound as claimed in Claim 8 or Claim 12, wherein R^8 represents a $-C_1-C_{18}$ alkyl group.

14. A compound as claimed in Claim 8, wherein R^9 represents a pyridinyl group and R^{10} represents a hydrogen atom.

15. Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-

(2-methylpropyl)propanoate,
1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinyl-methyl)phenylsulphonyl)propane,
1-Ethoxy-2-(2-methylpropyl)-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)butane,
1-Ethoxy-2-benzyl-3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl)pentane,
1-Methyl-1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)-2-(furan-2-yl)-4-methylpentane,
3-Acetoxy-5-methyl-2-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)-phenylsulphonyl)hexane,
3-Ethylcarbamoyl-5-methyl-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinyl-methyl)phenylsulphonyl)hexane,
Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylcarbonyl)-2-(2-methylpropyl)butanoate,
1-(4-(1H-2-Methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)-2-(3-ethyl-1,2,4-oxadiazol-5-yl)-4-methylpentane,
Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-4-benzthiazol-2-yl-5-methylhexanoate,
1-Heptadecanoyl-2-(2-cyclopentylmethyl)-3-(4-(1H-2-methylimidazo[4,5-c]-pyridinylmethyl)phenylsulphonyl)-3-methylbutane,
N-2-Pyridinyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenyl-sulphonyl)-2-(1-methylpropyl)propionamide,
i-Propyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(cyclopropylmethyl)hex-5-enoate,
1-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-thienyl)-3-(4-fluorophenyl)ethane,
Ethyl 3-(4-(1H-2-methylimidazo[4,5-c]pyridinylmethyl)phenylsulphonyl)-2-(2-methylpropyl)butanoate,

or a salt of such a compound.

16. A compound as claimed in any one of Claims 1 to 15 for use in human or veterinary medicine, particularly in the management of diseases or conditions mediated by platelet activating factor.

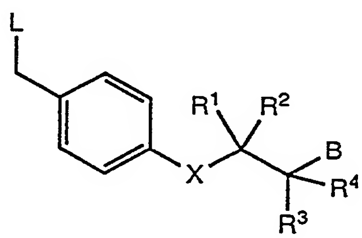
17. The use of a compound as claimed in any one of Claims 1 to 15 in the preparation of an agent for the treatment or prophylaxis of diseases or conditions

mediated by platelet activating factor.

18. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of Claims 1 to 15 and a pharmaceutically and/or veterinarily acceptable carrier.

19. A process for preparing a compound of general formula I as defined in Claim 1, the process comprising:

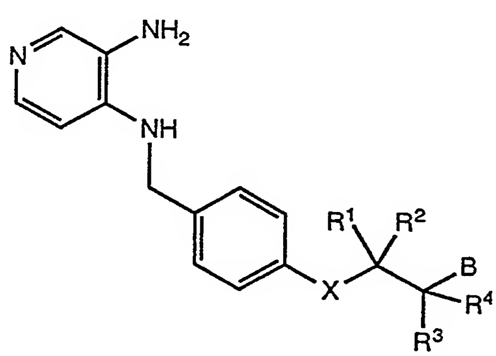
(a) treating 2-methylimidazo[4,5-c]pyridine with a base followed by a benzyl derivative of general formula II



II

wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy; or

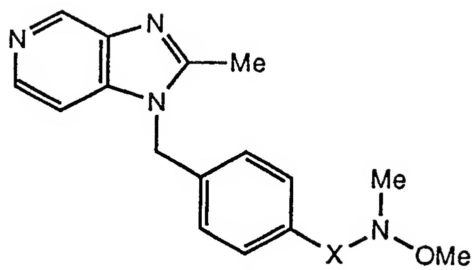
(b) treating a diamino derivative represented by general formula III



III

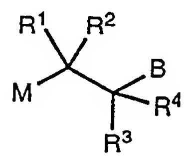
wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, with acetic acid or a suitable derivative thereof; or

(c) treating an amido or sulphonamido derivative represented by general formula IV



IV

wherein X is as defined in general formula I, with a compound of general formula V

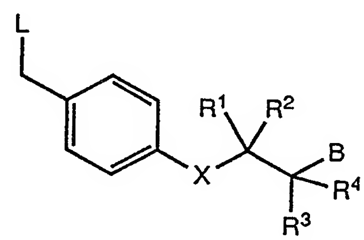


V

wherein R^1, R^2, R^3, R^4 and B are as defined in general formula I, and M is MgBr or Li; or

(d) optionally after step (a), step (b) or step (c) converting, in one or a plurality of steps, a compound of general formula I into another compound of general formula I.

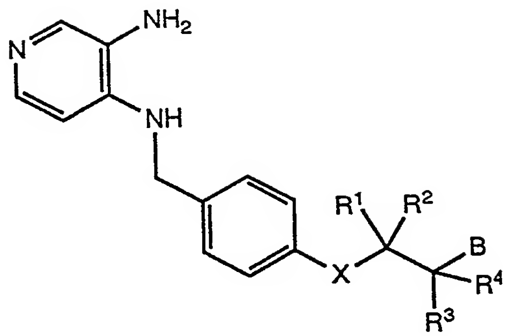
20. A benzyl derivative of general formula II



II

wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I, and L is chloro, bromo, iodo, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy.

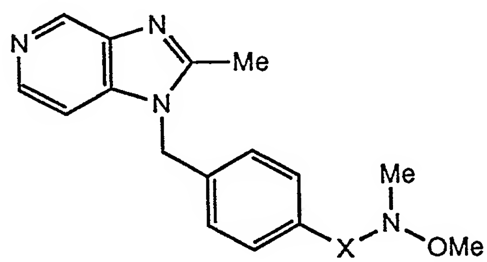
21. A compound of general formula III



III

wherein R^1, R^2, R^3, R^4, X and B are as defined in general formula I.

22. A compound of general formula IV



IV

wherein X is as defined in general formula I.

23. A method for the treatment or prophylaxis of diseases or physiological conditions of humans or mamalian animals mediated by platelet activating factor, comprising administering to the patient an amount of a compound as claimed in any of claims 1 to 15 effective to antagonise the effects of platelet activating factor on target cells responsible for such diseases or physiological conditions.

Patents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search Report)

Application number

GB 9302730.8

Relevant Technical fields

(i) UK Cl (Edition L) C2C CQN CQT CRA CRG CUL

(ii) Int Cl (Edition 5) C07D

Search Examiner

D S LUCAS

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASE: CAS ONLINE

Date of Search

Documents considered relevant following a search in respect of claims 1 TO 19 AND 23

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
A	WO 91/17157 A (BRITISH BIO-TECHNOLOGY LTD) - see compounds 30-37 on page 9 and Examples 30-37	1-19 and 23

Category	Identity of document and relevant passages	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family, corresponding document.

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).

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